SURGERY DECEMBER 1960
Gynecology & Obstetrics VOLUME 111
NUMBER 6

THE FATE OF HOMOGRAFTS AND PROSTHESES OF THE HUMAN AORTA

BÉLA HALPERT, M.D., F.C.A.P., MICHAEL E. DE BAKEY, M.D., F.A.C.S., GEORGE L. JORDAN, JR., M.D., F.A.C.S., and WALTER S. HENLY, M.D., Houston, Texas

EXPERIMENTAL and clinical investigations during the past half century have established the feasibility of implantation of vascular homografts. It was learned fairly recently that healing at the suture lines would occur even in aortas with atherosclerotic, thromboobliterative, or luetic changes. Thus, replacement of impaired segments of the human aorta by homografts became a standard surgical procedure and in many instances was immediately life-saving.

Morphologic studies on 10 human aortic homografts in place up to 12 months revealed no atherosclerotic change in the grafts. Subsequently, in 4 human aortic homografts that were in place up to 30 months, the walls were found to be weakened by alterations in the media of the grafts. These were due to a gradual diminution and interruption of the elastic fibers. Thus, the need for a suitable prosthesis was clearly manifest and various materials with different physical properties were introduced. The long-term behavior of aortic homografts and prostheses has been investigated experimentally under ordinary conditions and in induced chronic hypercholesterolemia. The present study deals with structural alterations in homografts of human aortas that were in place from 24 to 80 months and with the changes in prostheses of human aortas that were in place from 3 to 43 months.

From the Department of Pathology and the Cora and Webb Mading Department of Surgery, Baylor University College of Medicine, and Veterans Administration Hospital, Methodist Hospital, and Jefferson Davis Hospital, Houston.

Supported in part by grants from the U. S. Public Health Service, H-3137 and HTS-5387, American Heart Association, Texas Heart Association, and Houston Heart Association.

MATERIAL AND METHODS

Included in this study were 13 human aortic homografts and 14 prostheses. Of the 13 homografts, 2 were in place for 24 months, 6 from 31 to 45 months, and 5 from 59 to 80 months. Of the 14 prostheses, 1 was orlon, in place for 10 months, 5 were nylon, in place from 12 to 43 months, and 8 were dacron, in place 3 to 25 months. When available, the aorta with the graft in place was photographed and representative portions from pertinent areas were taken for microscopic study. These were embedded in paraffin or celloidin and consecutive micro-

scopic preparations were stained with hematoxylin and eosin, Masson's trichrome, and Weigert's elastic tissue stains.

HOMOGRAFTS

Aortic Homografts 24 Months After Implantation

CASE 1. A 54 year old white man was admitted with a blood pressure of 200/100 millimeters of mercury. An angiocardiogram revealed an aneurysm of the thoracic aorta just below the left subclavian artery. On 15 September 1955, a dissecting aneurysm of the descending thoracic aorta was excised and the aorta reconstructed by a freeze-dried homograft. The patient was discharged on the twentieth day after operation and returned to his usual activities. The hypertension persisted. On 21 September 1957, at home, a sudden exsanguinating hemorrhage through the mouth occurred and the patient died. Authorization for examination was limited to removal of the thoracic aorta.

The specimen was a segment of the aorta, 22 centimeters long, including the arch and proximal thoracic portion. The homograft was located just below the origin of the left subclavian artery and was 6 centimeters long. At the upper suture line there was dissolution of the substance with clotted blood surrounding the external surfaces. In the distal portion of the aorta a tubular structure, 4 centimeters in circumference, was surrounded by an outer wall.

In microscopic preparations from the upper suture line the frayed ends of the elastic fibers were noted. Along the suture line between the aorta and the homograft was a cleft filled by an amorphous coagulum that stained red with Masson's stain with no sign of organization.

CASE 2. A 41 year old white man was admitted with severe headache for 2 days. He had been treated for peptic ulcer for the past 2½ years. At the time of admission the blood pressure was 258/130 millimeters of mercury. Both femoral pulses were absent. In an angioaortogram the column of dye ended abruptly at the level of the first lumbar vertebra. A translumbar aortogram disclosed complete occlusion of the abdominal aorta and of the left renal artery. On 15 October 1954, the abdominal aorta including the bifurcation was resected and a proximal thromboendarterectomy to the level of the left renal artery and a distal thromboendarterectomy of the left external iliac artery and a bilateral sympathectomy were performed. The continuity of the aorta was re-established by a reconstituted freeze-dried aortic homograft. Gastric resection with gastroduodenostomy for chronic peptic ulcer of the stomach and appendectomy were also performed. Later, an intravenous pyelogram revealed no visualization of the left kidney. The patient was discharged from the hospital 12 November. On 27 October 1956, while at work, he had a sudden severe precordial pain that radiated down the left arm. Electrocardiogram revealed an anterior myocardial infarction and the patient died in the hospital.

At necropsy, the left kidney was about one-half the size of the right and weighed 90 grams. In the inferior pole was a wedge-shaped healed infarct, 2 by 1 centimeters. The heart weighed 590 grams. There was myocardial infarction, old and recent, in the anterior and septal portions of the left ventricle. In the thoracic and proximal abdominal aorta were numerous scattered atherosclerotic areas. The abdominal aorta, 4 centimeters below the renal arteries and including the bifurcation to 1 centimeter above the branching of the common iliac arteries, was replaced by a homograft. The lines of the anastomoses appeared intact, the black silk sutures shining through. There was a slight dilatation of the aorta just proximal to the upper line of anastomosis. A few atheromatous plaques were noted nearby. In the left renal artery near its origin was an aneurysmal dilatation, 2 centimeters in diameter, containing an organizing thrombus. Distal to this the lumen was obliterated. The lumen of the left internal iliac artery was occluded by a recent thrombus.

Microscopically, in a hematoxylin and eosin preparation of the homograft, the inner third was composed of a pink hyalin-like acellular fibrillar substance. External to this were coarse collagenous bundles, more loose peripherally, and infiltrated with many lymphocytes, some plasma cells and large mononuclear cells. At the line of anastomosis suture material was noted. Some slitlike spaces and large mononuclear cells with foamy cytoplasm were in focal areas in the intima and media of both the host and graft portions. Cell nuclei were noted in the host portion of the media but were absent in the homograft.

Aortic Homografts 31 to 45 Months After Implantation

CASE 1. A 69 year old white man was operated on 1 August 1955, when an abdominal aortic aneurysm was resected and a homograft inserted. The patient was discharged about 2 weeks later. On March 8, 1958, 31 months after operation, the patient died. Examination was restricted to the abdominal organs.

The homograft extended 7 centimeters upward from the bifurcation and 3 and 4 centimeters, respectively, into the common iliac arteries. There were large atheromatous plaques in the aorta proximal to the homograft and occasional raised yellow areas in the graft portion (Fig. 1).

Microscopically, in a cross section of the homograft 4 centimeters above the bifurcation, the graft portion constituted the inner one-half of the width of the wall with wavy elastic fibers condensed or spread apart. Coarse collagenous bundles formed the rest of the wall (Fig. 2).

CASE 2. A 64 year old white woman was operated on 10 May 1955, when an abdominal aortic aneurysm was resected. The homograft inserted extended from below the origin of the renal arteries to the bifurcation.

FIG. 1.

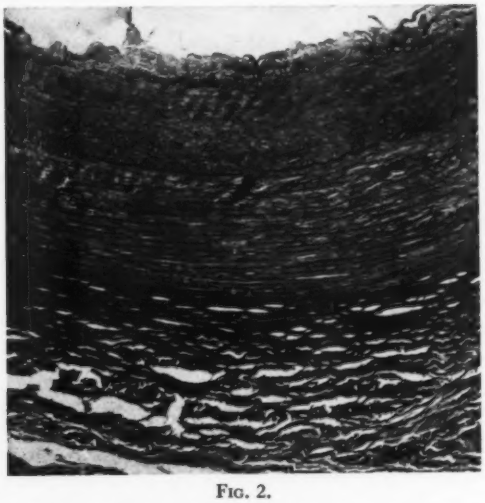


FIG. 2.

FIG. 1. The abdominal aorta with the homograft, in place for 31 months. Large atheromatous plaques are in the aorta and occasional raised yellow areas in the graft.

FIG. 2. Microscopic preparation from the graft in Figure 1. The graft portion constitutes about one-half of the width of the wall. The elastic fibers are condensed or spread apart. Weigert's elastic tissue stain, ×54.

On 18 June 1956, 13 months later, an aneurysm that developed in the graft was resected and the first homograft was replaced with a bifurcation homograft. On 21 August 1957, 14 months after this operation, an aneurysm of the second homograft was resected and a dacron prosthesis inserted, leaving in place about 4 centimeters of the proximal portion of the second homograft. The patient continued to have hypertension with a blood pressure of 200/120 millimeters of mercury. She died 20 February 1959 from rupture of the retained portion of the second homograft that had been in place 32 months.

At necropsy there was massive retroperitoneal, intraperitoneal, and bilateral pleural hemorrhage from a tear 0.5 centimeter in diameter in the homograft. The homograft was 4 centimeters long and was sutured to a dacron bifurcation prosthesis 4 centimeters above the bifurcation. The prosthesis was 11 centimeters long.

Microscopically, in a preparation stained with hematoxylin and eosin, the media of the homograft was narrow and extensively replaced by atheromatous change and calcific deposits. On the intimal surface amorphous coagulum was noted with few cell nuclei. In the adventitia massive extravasation of blood obliterated the pattern.

CASE 3. A 62 year old white man was admitted with a pulsating abdominal mass that had been enlarging for 2 years. On 26 May 1955, an abdominal aneurysm that extended from below the origin of the renal arteries and involved both common iliac arteries was resected and replaced by a homograft. This graft had been prepared by suturing together thoracic and abdominal segments. The patient was discharged 18 days later. He was well until 11 June 1958, when he died of massive hemorrhage into the intestine, 37 months after operation.

Necropsy revealed a communication between the proximal portion of the homograft and a loop of small intestine with massive hemorrhage into the lumen of the gut. The aorta was dilated, tortuous, with extensive atherosclerotic change. The bifurcation homograft extended from 2 centimeters below the origin of the renal arteries into the common iliac arteries. Two centimeters distal from its upper margin was communication between the aorta and small intestine.

FIG. 3.

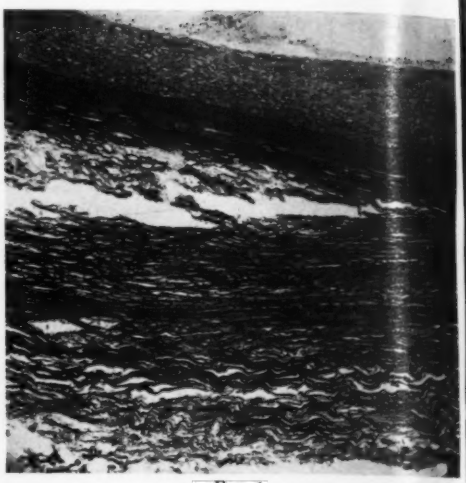


FIG. 4.

FIG. 3. The homograft, in place for 44 months, is located 6 centimeters below the superior mesenteric artery and extends 2 centimeters into each of the common iliac arteries. Atherosclerotic changes are extensive in the host portion. Only occasional plaques are in the graft.

FIG. 4. Microscopic preparation from the graft in Figure 3. The intimal zone is about one-half of the width of the media and composed of a fibrillar convoluted substance sharply demarcated by an inner elastic lamina. The inner third of the media is composed of compact elastic fibers, the outer two-thirds of loosely arranged fibers. In a focal area the media is interrupted by an amorphous plaque that disrupts and frays the elastic fibers. The adventitia is almost the combined width of the intima and media. Weigert's elastic tissue stain, ×54.

The graft was discolored and the wall appeared to be mostly replaced by adjacent tissue.

Microscopically, in the graft portion of the aorta on the luminal surface was a loose coagulum containing some large mononuclear cells with foamy cytoplasm. To this, in areas, clotted blood was attached. This intimal zone was about the width of the homograft. The homograft was composed of wavy elastic fibers. In one portion the elastic fibers were frayed and interrupted by an amorphous substance containing slitlike spaces. The graft was surrounded by a zone of coarse collagenous bundles as wide as or wider than the intimal and medial zones.

CASE 4. A 47 year old white woman was admitted because of intermittent claudication of the right lower extremity for 4 months. On 22 September 1955, the occluded segment of the abdominal aorta and its bifurcation were resected and replaced by a homograft. The patient was readmitted and aortography on 30 January 1959 revealed complete occlusion of the right iliac artery and marked atherosclerotic change in the left. The upper anastomosis of the aortic homograft was excised 40 months after implantation, with a dacron bypass prosthesis inserted to restore peripheral circulation.

The specimen obtained was a segment of the right limb of the bifurcation homograft, 2 centimeters long. In its distal portion were black silk sutures.

In microscopic preparations a lacelike loose coagulum containing occasional large mononuclear cells was attached to a broad intima composed of a cellular hyalinizing fibrous connective tissue. This was bordered by the media composed of closely packed elastic fibers with streaks of wavy lines toward the intima. The surrounding adventitia, made up of coarse collagenous bundles, equalled the width of the media.

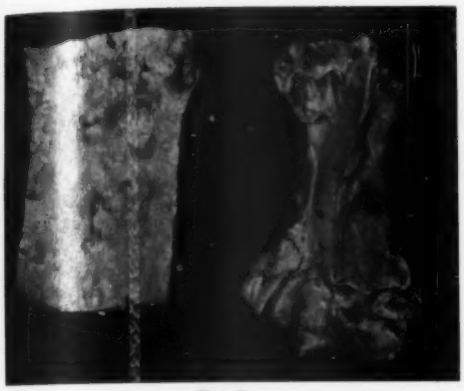


FIG. 5.

FIG. 5. Homograft in place 62 months extends 7 centimeters upward from the bifurcation and 2 centimeters into each of the common iliac arteries. Atherosclerotic changes are in the host aorta. Intimal surface is smooth.

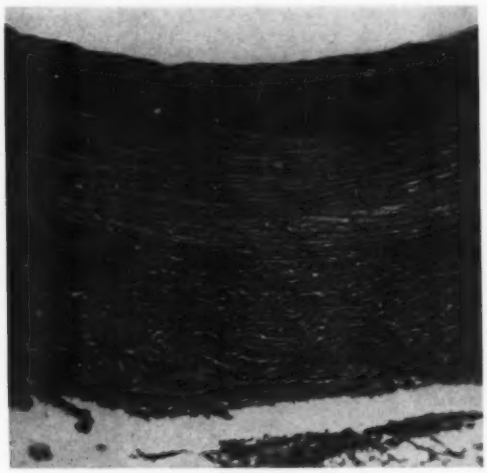


FIG. 6.

FIG. 6. Microscopic appearance of the graft in Figure 5 at its midportion. An inner elastic lamina delimits a delicate line of intima. The elastic fibers of the media are closely spaced in the inner portion and more loose in the outer portion. The adventitia is almost the width of the media. Weigert's elastic tissue stain, ×36.

CASE 5. A 46 year old physician was admitted with an abdominal aortic aneurysm noted 5 months previously. On 23 April 1956, the aneurysm, 11 by 6 centimeters, was resected and a bifurcation homograft inserted. The patient was discharged 14 days later. He died suddenly of myocardial infarction 1 January 1960, 44 months after operation.

The postmortem specimen received consisted of the abdominal aorta. The homograft was located 6 centimeters below the superior mesenteric artery extending 2 centimeters into each of the common iliac arteries. Extensive atheromatous changes were noted in the host portion for a length of 4 centimeters just above the upper suture line. Occasional plaques were seen also in the homograft (Fig. 3).

Microscopically, the intimal zone was about one-half the width of the media and was composed of fibrillar convoluted acellular substance sharply demarcated by an inner elastic lamina. The inner third of the media was composed of compact elastic fibers and the outer two-thirds of loosely arranged fibers. In focal areas the media was interrupted by amorphous plaques that disrupted and frayed the elastic fibers. The adventitia was almost the combined width of the intima and media and was composed of coarse collagenous bundles (Fig. 4).

CASE 6. A 55 year old white man was admitted with pain and a pulsatile mass in the abdomen. Resection of an aneurysm of the abdominal aorta with replacement by an aortic bifurcation homograft was performed 29 June 1954. Subsequently, the patient was treated for hypertension. He died quietly 20 March 1958, 45 months after operation.

The postmortem specimen received consisted of the abdominal aorta 4 centimeters above the bifurcation and 5 centimeters each of the common iliac arteries. Corresponding portions of the inferior vena cava and of the common iliac veins were attached. On the intimal surface of the aorta and common iliac arteries there was no clear demarcation between host vessel and homograft. The surfaces of both were covered with atherosclerotic plaques, more marked in the common iliac arteries 1.5 centimeters below the bifurcation and extending for a length of 1.5 centimeters. The changes were most marked in the host portions of the common iliac arteries.

Microscopically, in a Weigert preparation, pale fibrillar substance formed a broad or narrow intimal zone. The elastic fibers of the media were diminished, frayed, and interrupted. The adventitia was broad or narrow and was composed of coarse collagenous bundles.

Aortic Homografts 59 to 80 Months After Implantation

CASE 1. A 67 year old white man was operated on 6 May 1955, when an abdominal aortic aneurysm was excised and a bifurcation homograft inserted. His blood pressure continued at 220/120 millimeters of mercury. On 5 April 1960, 59 months after operation, a celiotomy was performed. The homograft appeared pliable with no gross evidence of atherosclerotic change or weakness. Dacron prostheses were inserted between the homograft and each of the renal arteries. Portions of the homograft were obtained.

In microscopic preparations giant cells of the foreign body type surrounded suture material. The intimal

FIG. 7

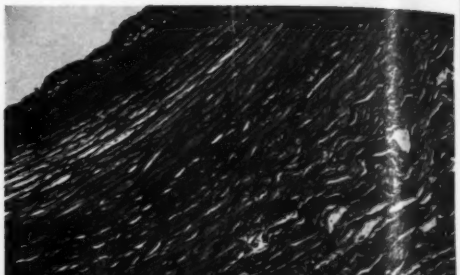


FIG. 8.

FIG. 7. Gross appearance of the homograft on its external and luminal surfaces 77 months after implantation. Atheromatous changes are marked adjacent to the suture line.

FIG. 8. Microscopic appearance of the homograft in Figure 7 just above the bifurcation. An intimal zone is barely discernible and is delimited from the media by wavy elastic fibers. The adventitia is about 3 times the width of the media. Weigert's elastic tissue stain, ×54.

surface was delimited by wavy elastic fibers and was devoid of covering cells. About one-third of the width of the homograft was composed of wavy delicate elastic fibers closely spaced in the inner half and more loose in the outer half. This was surrounded by a zone of coarse collagenous bundles.

CASE 2. A 44 year old white woman was admitted in November 1953 because of thrombosis of the distal aorta. A bifurcation homograft was inserted. The patient was treated with radioactive phosphorus for polycythemia vera. She was readmitted because of progressively increasing claudication and on 6 November 1958, 60 months after insertion, the homograft that was completely occluded in the right iliac artery and almost completely in the left was excised and a dacron bypass prosthesis was inserted.

Microscopically, the luminal surface of the removed portion of the homograft was covered by clotted blood with erythrocytes among masses of amorphous coagulum. This was bordered by a layer of fibrillar tissue. A zone of closely spaced elastic fibers made up the media. The width of this zone was less than that of the intimal zone. The adventitia was composed of coarse collagenous bundles.

CASE 3. A 65 year old white man was admitted with an abdominal aortic aneurysm confirmed by translumbar aortography. On 6 November 1952, the aneurysm was resected and a homograft inserted. Arterial insufficiency was later noted in the right leg. On 26 October 1953, because of complete occlusion of the right common iliac artery, the old homograft was replaced by a new one. The patient was well except for some peripheral arterial insufficiency in the arms and legs. He died of myocardial infarction 15 December 1958, 62 months after rehomografting.

The postmortem specimen disclosed that the homograft extended 7 centimeters upward from the bifurcation and 1 centimeter into one common iliac artery and 2 centimeters into the other. The intimal surface of the graft was smooth with no visible atherosclerotic change. Such changes were marked in the aorta and in the iliac arteries (Fig. 5).

Microscopically, in a Weigert preparation from the center of the homograft, the inner elastic lamina

delimited a delicate line of intima. The media was composed of elastic fibers closely spaced in the inner portion and more loose in the outer portion. The adventitia, composed of coarse collagenous bundles, was the width of the media (Fig. 6).

CASE 4. A 56 year old white man was admitted with a history of claudication of the left leg and without femoral pulses. On 14 September 1953, the terminal 2 centimeters of the occluded aorta and 3 centimeters of each of the common iliac arteries occluded by thrombi were replaced with a bifurcation homograft. The patient was readmitted for the last time, acutely ill in respiratory distress, and died 8 February 1960, 77 months after operation.

At necropsy there were marked emphysema with honeycombing of both lungs and arteriolar nephrosclerosis and cardiac hypertrophy. The homograft was patent. There were marked atherosclerotic changes in the aorta above the homograft and to a lesser degree also in the graft (Fig. 7).

Microscopically, in a Weigert preparation from the homograft just above the bifurcation, a barely discernible intimal zone was delimited from the media by wavy elastic fibers. The media varied slightly in width and was composed of closely spaced delicate elastic fibers. Dissolution of the elastic fibers with atherosclerotic changes was noted in occasional areas. These atherosclerotic changes were similar to those in a preparation from the adjacent host portion. The adventitia was made up of coarse collagenous bundles and was about 3 times the width of the media (Fig. 8).

CASE 5. A 52 year old white woman was operated on 10 August 1953, at which time an abdominal aortic aneurysm was resected and replaced by a bifurcation homograft. She was well until 1959 when persistent hypertension developed with a blood pressure of 220/100 millimeters of mercury. She was again admitted 10 April 1960, when an aortogram revealed stenosis of the left renal artery near its origin and patency of the homograft with no evidence of dilatation. The next day a dacron bypass prosthesis was inserted between the homograft and the left renal artery, and a portion of the homograft was excised.

Microscopically, the inner surface of the graft was indefinitely delimited by condensation of incomplete elastic fibers. Beneath this in a narrow zone were atherosclerotic changes and strands of frayed, frequently interrupted, elastic fibers. This was surrounded by an incomplete band of elastic fibers about one-third of the width of the inner zone. On the outside there were coarse collagenous bundles with occasional elastic fibers between them forming a zone about four times as wide as the remains of the homograft (Fig. 9).

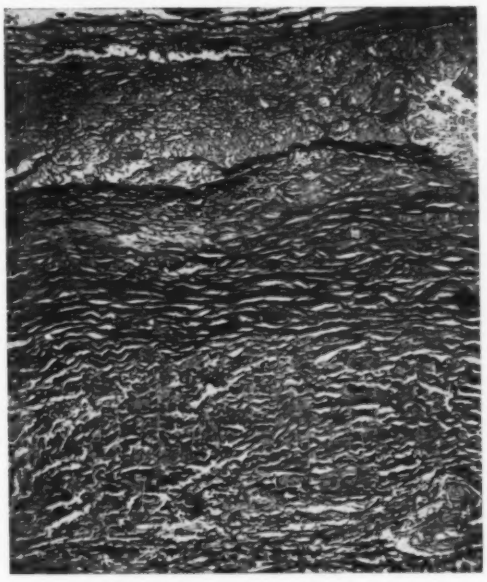


FIG. 9. Microscopic appearance of a homograft in place for 80 months. The inner surface is indefinitely delimited by condensation of incomplete elastic fibers. Beneath in a narrow zone are atherosclerotic and calcific changes and strands of frayed elastic fibers surrounded by a narrow band of elastic fibers. Coarse collagenous bundles with occasional elastic fibers form the outer layer about 4 times as wide as the remains of the homograft. Weigert's elastic tissue stain, ×54.

A survey of the clinical data reveals that of the 13 patients with aortic homografts in place from 24 to 80 months, 4 patients are alive, portions of their grafts having been resected when bypass operations were performed. Of the 9 patients who died, in 3 death was attributable to failure of the graft. In 1 of these, the only homograft that replaced a dissecting aneurysm in the thoracic aorta, dissection occurred in the homograft. In 1, death was due to perforation of the homograft into the small intestine and to massive hemorrhage into the intestinal tract. In the third, rupture of the homograft occurred with massive hemorrhage. Of the other 6, one patient died of pulmonary insufficiency with cardiac failure; the others of myocardial infarction.

PROSTHESES

Orlon Prosthesis 10 Months After Insertion

CASE 1. A 60 year old white man was admitted 31 March 1955, and an abdominal aortic aneurysm

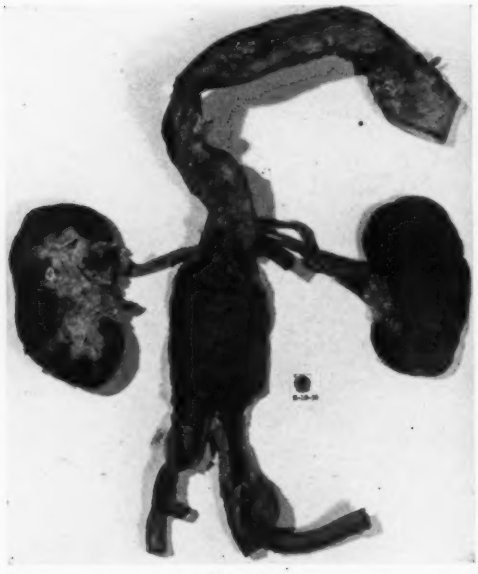


FIG. 10.

FIG. 10. Orlon prosthesis in place for 10 months. It extends from below the origin of the renal arteries and 1 centimeter into the left and 3 centimeters into the right common iliac arteries. The intimal surface is smooth with the suture lines shining through.

FIG. 11.

FIG. 11. Microscopic appearance of the orlon prosthesis in Figure 10. The luminal surface is bordered by a narrow band of amorphous coagulum and fibrous connective tissue that continues into septa between orlon fascicles. Between the inner and outer rows is a broader strip of fibrous connective tissue; a still broader zone surrounds the prosthesis. Weigert's elastic tissue stain, ×18.

was resected and replaced with an orlon prosthesis. Subsequently, he was treated for hypertension and was readmitted 7 January 1956. He died 21 January 1956, with massive left frontoparietal subdural hemorrhage.

At necropsy the orlon prosthesis extended from below the origin of the renal arteries and 1 centimeter into the left and 3 centimeters into the right common iliac arteries. The lumen was patent, and the intimal surface smooth with the suture lines shining through. There were some atheromatous plaques in the host aorta and in the common iliac arteries (Fig. 10.).

In microscopic preparations, along the suture lines an amorphous coagulum covered the inner surface. The underlying intima was broadened with extensive hyalin change. The narrow media contained a few elastic fibers. Giant cells of the foreign body type were noted around the suture material. The orlon fibers were in fascicles of about 100 each. Between the fascicles were delicate or broad connective tissue septa. These contained capillaries, lymphocytes, plasma cells, large mononuclear cells and, adjacent to the fibers, huge multinucleated giant cells of the foreign body type. The luminal surface was bordered by a narrow band of amorphous coagulum and fibrous connective tissue that continued into the septa between the fascicles of the orlon fibers. Between the inner and outer rows of the fascicles was a broader strip of fibrous connective tissue. A still broader zone of hyalinizing fibrous connective tissue nearly the width of the prosthesis surrounded the fabric on the outside (Fig. 11).

Nylon (Edwards-Tapp) Prostheses 12 to 43 Months After Insertion

CASE 1. A 64 year old white man was admitted 1 January 1957, and a pulsating abdominal aortic aneurysm, discovered 2 months earlier, was resected and a nylon bifurcation prosthesis inserted. The patient was discharged 12 days later. He was well until 26 December 1957, when he died suddenly, 12 months after operation.

At necropsy marked arteriolar nephrosclerosis and cardiac hypertrophy were noted. The heart weighed 625 grams. There was marked scarring of the myocardium involving the anterior two-thirds of the left ventricle and septum. The thoracic aorta was tortuous with the wall of uneven width. There was atheromatous change in the intimal surface. The involvement was more marked past the arch. The nylon prosthesis started 3.5 centimeters below the origin of the superior mesenteric artery and extended for a length of 6 centimeters to the bifurcation and 4 centimeters into each common iliac artery. A thin film of coagulum covered the surface. No microscopic preparations were available for study.

FIG. 12.

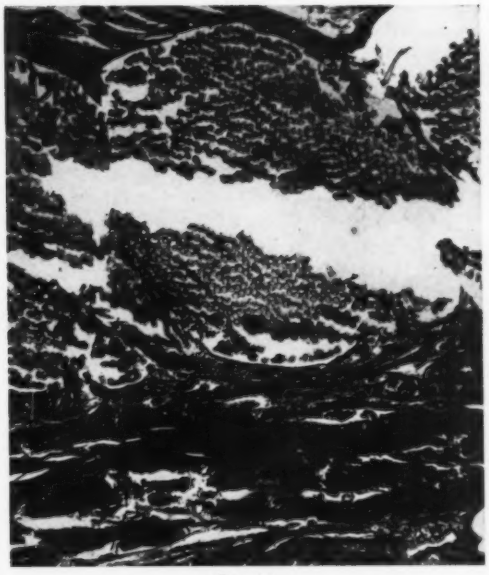


FIG. 13.

FIG. 12. Portion of the abdominal aorta and common iliac arteries replaced by a nylon prosthesis 7 centimeters long. The intimal surface is smooth with the pattern of the fabric shining through. The suture line is intact.

FIG. 13. Microscopic appearance of the nylon prosthesis in Figure 12. Dense hyalinizing fibrous connective tissue covers the inner surface near the suture line, thinning gradually toward the prosthesis. A broad zone of hyalinizing fibrous connective tissue surrounds the nylon fibers. Weigert's elastic tissue stain, ×54.

CASE 2. A 63 year old white man was operated on 18 March 1957, when an abdominal aneurysm was resected and a woven nylon bifurcation prosthesis inserted. The patient died 4 April 1958, 12½ months later, with myocardial infarction.

At necropsy the heart weighed 575 grams and there was left posteroseptal infarction. In the abdominal aorta the prosthesis extended from 2 centimeters below the renal arteries into each of the common iliac arteries. The suture lines were intact and the inner surface was smooth. Atheromatous plaques were noted in the arch and thoracic portions of the aorta. No microscopic preparations were available from the graft.

CASE 3. A 69 year old white man was admitted with an abdominal aortic aneurysm, discovered 2 months earlier when a cholecystectomy was performed. The aneurysm was resected 8 January 1957, and a bifurcation nylon prosthesis inserted. He was discharged 2 weeks later. On 16 November 1958, 22 months later, while working on the roof of his house he fell and died of dislocation of the first and second cervical vertebrae, contusion of the upper cervical spinal cord, and multiple subdural hemorrhages.

The postmortem specimen received consisted of the arch and the thoracic and abdominal portions of the aorta including the common and external iliac arteries. The intimal surfaces of the arch and the thoracic portion were covered with closely spaced atherosclerotic plaques. The terminal portion of the abdominal aorta was replaced for a length of 7 centi-

meters by a nylon prosthesis that extended into both common iliac arteries. The lumen was patent and the intimal surface smooth with the pattern of the fabric shining through. All suture lines were intact (Fig. 12).

In microscopic preparations sclerotic and calcific changes were extensive in the media of the aorta adjacent to the suture line. Giant cells of the foreign body type were abundant around both the suture material and the round nylon fibers. The prosthesis was about 50 fibers thick. Dense hyalinizing fibrous connective tissue covered the inner surface of the suture line, thinning gradually toward the prosthesis and disappearing, leaving the nylon fibers uncovered. Dots of coagulum stained red in Weigert's preparation were scattered among the nylon fibers. A broad zone of hyalinizing fibrous connective tissue surrounded the nylon fibers on the outside (Fig. 13).

Case 4. A 57 year old white man was operated on 14 March 1957, when the distal abdominal aorta and common iliac arteries were resected because of thrombo-obliterative disease and a small aneurysmal dilatation of the aorta. A woven nylon bifurcation prosthesis was inserted. Subsequently, the hypertension persisted, and intermittent claudication developed in the right lower limb. An aortogram revealed stenosis of the left renal artery and aneurysmal dilatation of the aorta just above the prosthesis and occlusion of the right superficial femoral artery. On 12 April 1960, 37 months after the first operation, the aneurysm and the prosthesis were excised and a dacron bifurcation prosthesis was inserted. A bypass to the left renal artery was also performed.

The specimen received consisted of a portion of abdominal aorta just below the renal arteries and of the nylon bifurcation prosthesis. The aneurysm was fusiform, 3.5 by 3 centimeters, with a friable inner lining. The suture line was intact and the inner surface of the graft was lined by a delicate film through which the fabric of the prosthesis could be seen. The external surface was covered by a layer of fibrous tissue.

Microscopically, a broad zone of pink coagulum with a pattern of a thrombus lined the inner surface. Between the nylon fibers were erythrocytes and occasional strands of fibrous connective tissue.

Case 5. A 66 year old white man was operated on 27 August 1956, when an abdominal aortic aneurysm was resected and replaced with a woven bifurcation nylon prosthesis. At the same time, an abdominal-perineal resection of the rectum for carcinoma was also performed. The patient was well until 17 March 1960, nearly 43 months after operation, when occlusion of the right limb of the graft occurred. At celiotomy an aneurysm of the nylon graft was noted at the bifurcation. A dacron prosthesis was used to bypass the aneurysm and a biopsy was taken from the prosthesis.

In microscopic preparations nylon fibers appeared spread apart by coagulum, clotted blood, and erythrocytes with apparent disruption of the arrangement of the fibers.

Dacron Prostheses 3 to 25 Months After Insertion

Case 1. A 68 year old white man was admitted with a pulsating mass, 12 by 12 centimeters, in the abdomen, noticed 8 years previously. On 6 September 1957, the abdominal aortic aneurysm was resected and a dacron prosthesis inserted. Cholecystectomy and appendectomy were also performed. The patient left the hospital 25 days after operation. He was well until 11 November 1957, when icterus developed which was attributed to viral hepatitis, and he died 13 December 1957, 3 months after operation.

The specimen obtained at postmortem examination consisted of the abdominal aorta. The dacron prosthesis commenced 2 centimeters below the origin of the renal arteries and extended 9 centimeters to the bifurcation and 3 and 4 centimeters, respectively, into the common iliac arteries. All suture lines appeared intact. On the inner surface in the distal 6 centimeters there was brown discoloration with a film of coagulum up to 0.3 centimeter thick.

In microscopic preparations sclerotic changes and calcific deposits were noted in the media of the aorta. Foreign body giant cells were scattered around the suture material. The intimal surface was covered by a broad zone of young connective tissue that faded over the prosthesis into a broad coagulum with some scattered cell nuclei. The dacron fibers appeared round, oval, or elongated. They were close together, separated at irregular intervals by coagulum or by loose or hyalinizing fibrous connective tissue containing some lymphocytes and plasma cells and many large mononuclear cells with brown granules in their cytoplasm. Giant cells of the foreign body type were few. A broad zone of hyalinizing fibrous connective tissue bordered the external surface of the prosthesis.

Case 2. A 65 year old white man was admitted on 9 August 1957. A ruptured abdominal aortic aneurysm was resected and a dacron prosthesis inserted. He was discharged 16 October 1957. The patient died of subdural hemorrhage on 17 November 1957, 3 months after operation.

The postmortem specimen received consisted of the abdominal aorta and the common iliac arteries. The intimal surface was covered with atherosclerotic plaques. Commencing 6 centimeters below the origin of the renal arteries the dacron prosthesis extended 3 centimeters to the bifurcation and replaced the left common iliac artery for 4 centimeters and the right for 7.5 centimeters. The suture lines were intact. The inner surface of the prosthesis was smooth and glistening with a transparent film of coagulum through which the weave of the fabric was discernible (Fig. 14).

In microscopic preparations from the suture line there were hyalin and atheromatous changes in the intima and media of the aorta. Giant cells of the for-

FIG. 14.

eign body type surrounded the suture material. They were huge along the outer surface of the prosthesis near practically every fiber. The dacron fibers appeared in slightly wavy streams. Coagulum or erythrocytes filled the spaces between them. Similar material formed an incomplete inner lining. Surrounding the prosthesis was a zone of dense hyalinizing fibrous connective tissue about half the width of the prosthesis (Fig. 15).

CASE 3. A 63 year old white woman was operated on 17 October 1958, when a thoracic aortic aneurysm was excised and a dacron prosthesis inserted. She was well until 20 March 1959, when she died from acute hepatitis, 5 months after operation.

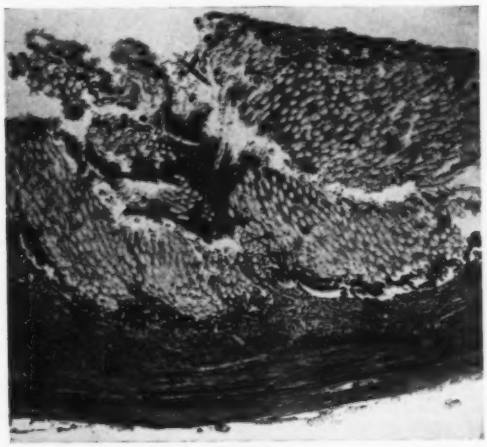


FIG. 15.

FIG. 14. Dacron prosthesis in place for 3 months commences 6 centimeters below the origin of the renal arteries and extends 3 centimeters to the bifurcation and replaces the common iliac arteries for a length of 4 and 7 centimeters, respectively. The suture lines are intact. The inner surface is smooth and glistening with a transparent film of coagulum through which the weave of the fabric is discernible.

FIG. 15. Microscopic appearance of the prosthesis in Figure 14. Hyalinizing fibrous connective tissue one-half the width of the prosthesis forms the external layer. Huge giant cells of the foreign body type surround the outer surface near practically every fiber. The dacron fibers are in slightly wavy streams. Coagulum or erythrocytes fill the spaces between them. Similar material forms an incomplete inner lining. Weigert's elastic tissue stain, ×54.

At necropsy the thoracic portion of the aorta was replaced by a dacron prosthesis that extended from the origin of the left subclavian artery for a length of 9 centimeters. The suture lines were intact. There was marked tree-bark appearance and stellate scarring of the proximal portion of the aorta. The aorta above and below the prosthesis was dilated with atherosclerotic change grafted upon the luetic aortitis. The inner surface of the graft was covered with a delicate film through which the ridges and fabric of the prosthesis were discernible.

In a microscopic preparation from the suture line, stained with hematoxylin and eosin, there was marked hyalin change in the host aorta. A narrow zone of pink coagulum covered the luminal surface. This contained a few elongated cell nuclei, particularly at intervals where the coagulum dipped between bundles of dacron fibers. The coagulum was noted also between the fibers. Huge giant cells of the foreign body type surrounded the dacron fibers on the outside. A narrow band of hyalinizing fibrous connective tissue separated the external surface from adherent lung.

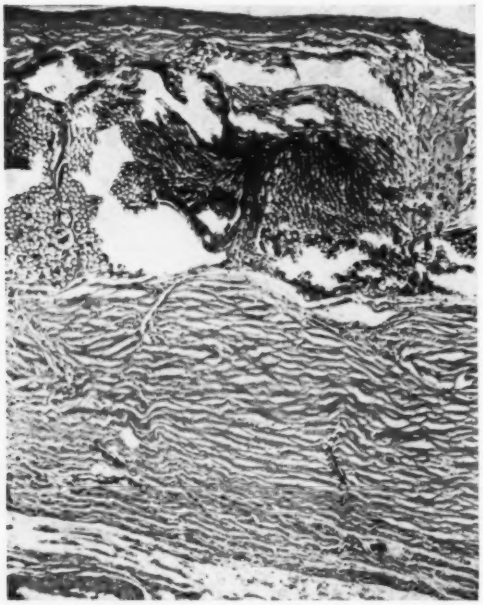


FIG. 16. Microscopic appearance of a dacron prosthesis in place 13½ months. On the inner surface is pink coagulum and fibrous connective tissue with hyalin change. The dacron fibers are cut transversely or obliquely. The connective tissue extends from the inner surface between bundles of dacron fibers to join a zone of connective tissue bordering the prosthesis from the outside. The bundles of dacron fibers are surrounded by giant cells of the foreign body type, some large mononuclear cells with brown granules in their cytoplasm, and lymphocytes and plasma cells. These surround the bundles from all sides except upon the inner surface. A broad band of hyalinizing fibrous connective tissue surrounds this zone on the outside and is as wide as the prosthesis. Hematoxylin and eosin, ×54.

CASE 4. A 64 year old white man was operated on 3 July 1958, when an aortofemoral popliteal dacron bypass was inserted for occlusive disease of the distal aorta and common iliac and femoral arteries. The patient died 22 August 1959, 13½ months after operation, from complications of cerebrovascular insuffiency.

At necropsy there was nephrosclerosis and cardiac hypertrophy. The heart weighed 500 grams and there was extensive left anterior, posterior, and septal scarring of the myocardium. A bilateral aortopopliteal dacron bypass was patent throughout its length. Both common and external iliac arteries as well as both of the hypogastrics were occluded by organized thrombi.

In microscopic preparations an inner zone of pink coagulum, fibrous connective tissue with hyalin change, and scattered cell nuclei bordered the inner surface of the prosthesis, the fibers of which were cut transversely or obliquely. The connective tissue extended from the inner surface between bundles of dacron fibers to connect with a zone of connective tissue bordering the prosthesis from the outside. The bundles of dacron fibers were surrounded by giant cells of the foreign body type, some large mononuclear cells with brown granules in their cytoplasm, and lymphocytes and plasma cells. These surrounded the bundles from all sides except upon the inner surface. The zone of cellular infiltration was bordered by a broad band of hyalinizing connective tissue on the outside as thick as the width of the fabric of the prosthesis. Along the suture line giant cells of the foreign body type surrounded suture material and adjacent fibers of the prosthesis (Fig. 16).

CASE 5. A 76 year old white man was operated upon 25 November 1957, when aneurysms of the abdominal aorta and of both common iliac arteries were resected and a dacron prosthesis was inserted. The patient recovered from the operation. Subsequently, personality changes developed, attributed to a cerebrovascular lesion. He became a feeding problem and died with uremia and acidosis 8 February 1959, nearly 15 months after operation.

At necropsy atheromatous change was noted in the aorta. The portion of aorta from 1 centimeter below the renal arteries and the common iliac arteries were replaced by a dacron prosthesis. This was 6 centimeters long to the bifurcation and 3 centimeters into the left and 4.5 centimeters into the right common iliac arteries. A coagulum covered the suture lines. A thin film of coagulum lined the inner surface of the prosthesis.

In microscopic preparations a coagulum of varying width covered the inner surface. There was no discernible connective tissue covering on the inner surface except near the suture line. Septa of connective tissue were noted between bundles of dacron fibers. A zone of hyalinizing fibrous connective tissue with some giant cells of the foreign body type adjacent to the fibers bordered the outer surface of the prosthesis.

CASE 6. A 66 year old white woman was operated on 21 August 1957, 14 months after insertion of a second aortic homograft. An aneurysm of the homograft was resected and a dacron prosthesis inserted so that about 4 centimeters of the proximal homograft were left in place. The patient died from rupture of the homograft on 20 February 1959, 18 months after insertion of the dacron prosthesis. No histologic studies were made of the prosthesis.

CASE 7. A 69 year old white physician was admitted 1 December 1957, with pain in the abdomen from a leaking abdominal aortic aneurysm. This was resected and a dacron prosthesis inserted. The patient was discharged 1 month later. He died of myocardial infarction 15 July 1959, 19½ months after operation.

The postmortem specimen received was the abdominal aorta from the level of the celiac artery. From just below the origin of the renal arteries a dacron

FIG. 17.

FIG. 17. Dacron prosthesis in the abdominal aorta in place for 25 months. On cross section of the midportion of the prosthesis a layer of connective tissue up to 0.6 centimeter wide surrounds the prosthesis. Atherosclerotic plaques are noted in the intima and media above the prosthesis extended to the bifurcation of the aorta. The luminal surface was covered with a film of coagulum up to 0.4 centimeter thick. Above the upper suture line was an aneurysmal widening of the wall to 3 centimeters in diameter. Here clotted blood was attached to the intimal surface. The suture line was covered by a thin film that easily separated from the underlying fabric. There were no plaques along the suture lines.

In microscopic preparations the inner surface of the prosthesis was lined by an almost even layer of coagulum nearly as thick as the prosthesis and having the pattern of a recent thrombus. The dacron fibers were subdivided by connective tissue septa about 30 fibers apart. The septa contained endothelium-lined spaces, apparently extravasated erythrocytes, and large mononuclear cells with brown granules in their cytoplasm. Giant cells of the foreign body type were few. On the outer surface of the prosthesis was a zone of dense hyalinizing fibrous connective tissue which was as wide as the intimal zone and the prosthesis combined.

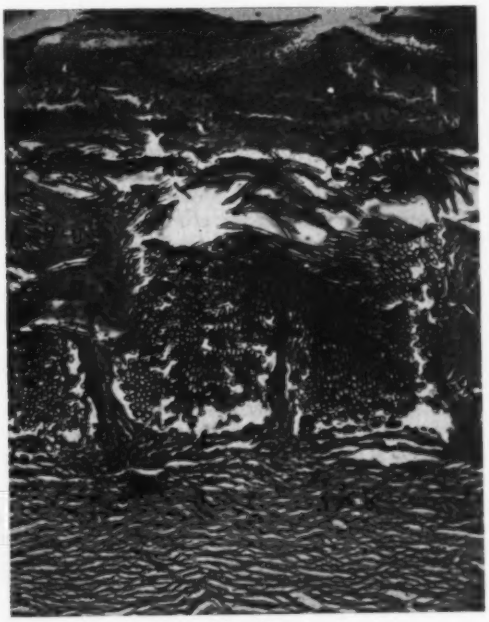


FIG. 18.

FIG. 18. Microscopic appearance of the prosthesis in Figure 17. A delicate layer of coagulum covers the inner surface and dips between bundles of fibers that are separated by connective tissue septa of varying widths. The septa broaden toward the outside continuing into a zone of hyalinizing fibrous connective tissue. Giant cells of the foreign body type and large mononuclear cells with rusty brown granules in their cytoplasm, lymphocytes, and plasma cells are adjacent to the dacron fibers. A broader zone of hyalinizing fibrous connective tissue surrounds the zone of cellular infiltration. Coarse collagenous bundles form an outer layer that is as wide as the prosthesis and the surrounding connective tissue combined. Hematoxylin and eosin stain, ×54.

CASE 8. A 48 year old white man was operated on 13 February 1958, when an abdominal aortic aneurysm was resected and replaced by a dacron bifurcation prosthesis. He was well until 16 March 1960, 25 months after operation, when he died suddenly of myocardial infarction.

The specimen received consisted of the distal portion of the thoracic aorta 11 centimeters to the celiac artery, the abdominal aorta including both common iliac arteries and the external iliac and hypogastric arteries. On transverse cut surfaces of the abdominal aorta 2 centimeters above the celiac artery occasional atheromatous plaques were noted in the intima and media. The anterior surface of the aorta and graft was obliterated by fibrous connective tissue so that the borderlines between the prosthesis and the host aorta could not be discerned. On cross section of the midportion of the graft was a layer of fibrous connective tissue 0.3 to 0.6 centimeter wide surrounding the prosthesis. The inner surface of the graft was smooth with a barely discernible film covering the fabric of the prosthesis. The upper and lower suture lines were intact (Fig. 17).

In microscopic preparations, around the circumference of the host aorta proximal to the prosthesis eccentric focal thickenings of atheromatous change were noted. On cross section of the midportion of the graft a delicate layer of coagulum covered the inner surface. This dipped between bundles of fibers that were separated by connective tissue septa of varying widths. The septa broadened toward the outside continuing into a zone of hyalinizing fibrous connective tissue. The septa as well as the zone toward the dacron fibers were infiltrated with giant cells of the foreign body type, large mononuclear cells with rusty brown granules in their cytoplasm, lymphocytes, and plasma cells. A broader zone of dense hyalinizing fibrous connective tissue surrounded the zone of cellular infiltration. Coarse collagenous bundles formed an outer layer. This was as wide as the prosthesis and its surrounding fibrous connective tissue combined (Fig. 18).

A survey of the clinical data of the 14 patients with aortic prostheses in place from 3 to 43 months reveals that 2 patients are alive. In the other 12, the immediate cause of death was not associated with their prostheses. The patient whose orlon prosthesis was in place for 10 months died of intracranial hemorrhage. Of the 5 patients with nylon prostheses in place from 12 to 43 months, 2 are alive, 2 died from myocardial infarction, and 1 from accidental fracture of the cervical vertebrae. Of the 8 patients with dacron prostheses that were in place from 3 to 25 months, 2 died from viral and acute hepatitis, respectively. Of the other six, 1 died from subdural hemorrhage, 1 from cerebrovascular insufficiency, 1 from uremia, 1 from rupture in the homograft, and 2 from myocardial infarction.

COMMENT

Studies in experimental animals and in man of the structural alterations in homografts and prostheses of the aorta provide information as to the manner in which they serve the purpose of replacing impaired portions of the aorta. Furthermore, it is now possible to compare the behavior of homografts with that of the various types of prostheses.

The homograft is an organic structure that originally served the purpose for which it is used again; however, when transplanted, it contains no living cells. Again in contact with the blood stream on the inside and with living tissue on the outside, it serves anew as a section of the "aortic pipeline." The immediate adaptation of the homograft is initiated by the passage of blood through its lumen in steady waves and by its intimate contact with the raw retroperitoneal tissues. The blood between the crevices of the suture lines and surrounding the graft offers nutrition for fibroblasts and endothelial cells, stimulating them to proliferate. Granulation tissue soon surrounds the graft.

Though the homograft is functionally and structurally adopted by its new environment, structural alterations occur consisting of a gradual reduction of the elastic fibers and of the ground substance of the media. The elastic fibers become condensed toward the luminal surface and looser toward the periphery. On the outside, the graft becomes encased in hyalinizing fibrous connective tissue that increases in width as the graft thins. Gradually the elastic fibers diminish and fragment. Their attrition and the appearance of atheromatous plaques further reduce and weaken the substance of the graft. These retrogressive changes in the graft are similar to those that were present in the host aorta at the time of implantation of the graft and that have since continued.

Most patients whose vascular lesions necessitate replacement have some metabolic deviation and hypertension. The homograft that is implanted into such an environment is exposed to constant pressure from within

that is usually higher than the normal systolic blood pressure. Therefore, the homograft eventually becomes affected in the same manner as the rest of the aorta. The abnormal stress is perhaps the principal factor that weakens the homograft's strongest structural elements, the elastic fibers. The longevity of the homograft depends on its structural makeup at the time of implantation as well as upon the conditions that prevail in its new environment. Under unfavorable circumstances its longevity will be short, under favorable conditions long. The attrition of the elastic fibers and of the ground substance of the graft and the apposition of the connective tissue from the outside proceed with varying speeds so that even after 80 months some remains of the homograft have been observed.

When chronic hypercholesterolemia was experimentally induced in the dog retrogressive changes developed in the previously inserted homograft sooner than in the host aorta. In the human, in whom a part of the abdominal aorta was resected because of atherosclerotic aneurysm or occlusive disease of the aorta and common iliac arteries, the atheromatous change in the host vessel was already extensive at the time the homograft was implanted. Under such circumstances the homograft usually did not manifest the degree and extent of retrogressive change present in the host aorta. Therefore, at the time of death from complications of the cardiovascular renal disease, the homograft frequently was the least involved portion of the aorta.

Whatever their longevity, homografts present disadvantages in procurement and preparation. Whatever the disadvantages of prostheses, they are available and easier to handle and appear to serve as well as homografts.

The prosthesis is a synthetic fabric composed of a mesh of fibers of varying diameters and distances from one another. At the time of insertion it becomes soaked with blood that fills the crevices between the fibers. The blood coagulates and the film of coagulum covers the outer surface. This becomes surrounded by tissues of the retroperitoneal space so that fibroblasts and endothelial cells gain access to the clotted blood on the outer surface of the prosthesis and also to the blood retained in the crevices between the fibers. In addition, granulocytes, lymphocytes, plasma cells, large mononuclear cells, and many giant cells of the foreign body type appear. The cells surrounding individual fibers or groups of fibers penetrate through the spaces to reach the inner surface of the prosthesis.

In microscopic preparations it is often difficult to preserve and observe the finer structure of the inner lining of the prosthesis. True intima with endothelial cells can be identified only over the suture line and not over the midportion of the graft. In those sections in which the inner lining can be studied the innermost layer appears to be composed of elongated cells, probably fibroblasts rather than endothelial cells. Lipid deposition on the inner surface has been produced experimentally in induced chronic hypercholesterolemia in dogs but has not been observed in man.

Eventually a slowly broadening zone of dense hyalinizing fibrous connective tissue encases the tube on the outside and forms a similar, more delicate layer on the inside. The foreign body reaction is adjacent to the fibers and is present only in the outer portions of the prosthesis. It appears, therefore, that porosity is an essential feature for the acceptance of the prosthesis by the host. Through its meshes cells of the host can penetrate. Our experience with impervious or closely woven prostheses indicates that too close a weave prevents the invasion and organization from the outside. Thus, a coagulum adheres to the inner surface of the prosthesis without being actually attached. Minimal trauma may, therefore, cause it to slip off and to occlude the lumen of the vessel. On the outside, the nonadherence of host tissue was particularly noted in an ivalon prosthesis removed from the femoral artery after 42 months. There was no growth of fibroblasts into the graft.

It might, therefore, be postulated that the ideal prosthesis still to be found will consist of a synthetic material, the fibers of which are interspersed with absorbable hemostatic fibers woven or knitted tightly enough to prevent blood loss at the time of insertion. Later, when the hemostatic fibers are absorbed, sufficient porosity will occur to allow satisfactory ingrowth of fibroblasts and endothelial cells, resulting in attachment of the prosthesis to the host tissues.

Studies of tensile strength were not made on the prostheses removed from the human. Clinical impressions, however, suggest that the results of animal experimentation in this regard are applicable. Thus, there has been actual rupture of ivalon prostheses as well as of nylon prostheses. Patients have been encountered in whom there was complete separation of the suture lines with the development of false aneurysms as a result of fraying of the distal ends. Attempt to suture this material at the time of secondary operations is fraught with difficulty and is hazardous. Teflon and dacron, however, have maintained their tensile strength for long periods and at the time of reoperation appeared to have essentially the same strength as when they were inserted.

SUMMARY

Structural alterations observed in 13 homografts of the human aorta in place from 24 to 80 months are recorded, and changes in 14 prostheses that were in place from 3 to 43 months.

In the homografts the changes were those of progressive attrition of the elastic fibers of the graft media with gradual apposition from the outside of hyalinizing fibrous connective tissue with coarse collagenous bundles. Sparse remains of the homograft were observed even as long as 80 months after implantation.

In the prostheses studied the changes observed were those of progressive encasement by hyalinizing fibrous connective tissue. While the ideal prosthesis is still to be found, the knitted dacron prosthesis appears to be satisfactory in most instances.

A CLINICAL STUDY OF CIRCULATING TUMOR CELLS IN MALIGNANT MELANOMA

MARVIN M. ROMSDAHL, M.D., Chicago, Illinois, JOHN F. POTTER, M.D., Washington, District of Columbia, RICHARD A. MALMGREN, M.D., ELIZABETH W. CHU, M.D., CLYDE O. BRINDLEY, M.D., and ROBERT R. SMITH, M.D., Bethesda, Maryland

THE PROBLEM of metastatic dissemination in neoplastic disease has received a great deal of attention as indicated by reports of numerous clinical and laboratory studies. Many investigations of modes of spread have been directed primarily at the practical aspects of metastases which are of concern to all physicians and especially to surgeons. In the past, much knowledge has been gained from morphologic interpretation of autopsy material and surgical specimens. More recently, emphasis has been placed on exploration of the mechanisms and dynamics of metastases by clinical and experimental studies and has resulted in the application of methods designed to determine certain physiologic phenomena. One such application has been the study of tumor cells from the blood of patients with cancer. Although the presence of cancer cells in the blood has been known for almost a century, in the past 6 years there has been greater interest in their identification and significance, as is reflected by the comprehensive report of Engell (2) in 1955 and the work of Cole (12), Fisher (5), and Moore and their associates. The study of metastatic spread by way of the blood has been made possible by technical improvements in the isolation and identification of malignant cells.

Invasion of veins and lymphatics by cancer was described in 1865 by Thiersch. In 1869 Ashworth reported the identification of abnormal cells in the peripheral blood of a patient which were recognized as being similar to those of the patient's multiple malignant skin tumors. Various investigators have used smears to demonstrate tumor cells in blood. In 1921 Quenzel tried unsuccessfully to identify tumor cells in blood after hemolysis of erythrocytes with distilled water. The first systematic attempts to demonstrate cancer cells from living patients were made by Pool and Dunlop in 1934. They identified tumor cells in venous blood from 17 of 40 cases of advanced carcinoma. In 1955 Engell found peripheral circulating tumor cells in 10 of 79 patients (13 per cent) with various operable malignant tumors and in 7 of 14 patients with inoperable carcinoma. He also found tumor cells in venous blood draining the site of cancer in 41 of 76 cases of rectal carcinoma and in 22 of 31 patients with carcinoma of the colon. He concluded that operative manipulation did not definitely increase the incidence of demonstrable tumor cells in the blood stream and that no data of prognostic value could be derived from finding cancer cells in the venous blood draining tumors. This latter conclusion is supported by his 5 to 9 year follow-up studies from which he learned that in 51 per cent of those patients who survived this period tumor cells were demonstrated in the blood at operation (3).

To learn more of the relationship between metastasis and circulating malignant cells, it was thought desirable to study a malignant tumor in which hemic dissemination is a

From the Surgery, Pathologic Anatomy, and General Medicine Branches of the National Cancer Institute, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda.

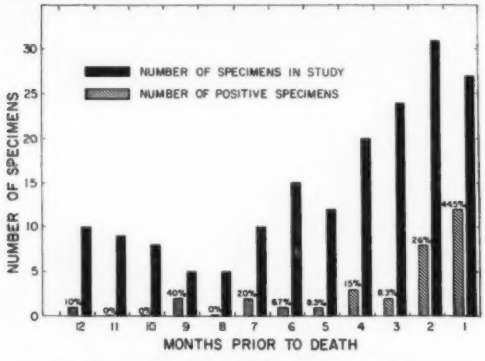


FIG. 1. Demonstration of peripheral circulating tumor cells in relation to stage of disease as determined by multiple blood specimens. Summary of examinations for peripheral circulating tumor cells in 28 patients with advanced malignant melanoma during a period 12 months prior to death.

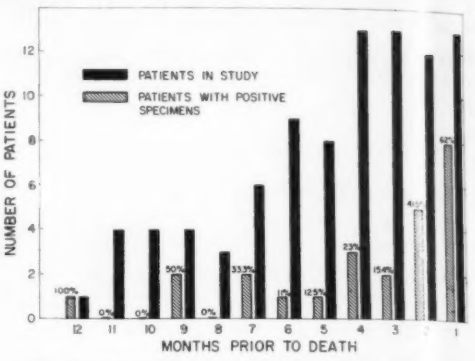


FIG. 2. The finding of peripheral circulating tumor cells in relation to stage of disease as determined for individual patients. Summary of patients with advanced melanoma studied for peripheral circulating tumor cells during a period 12 months prior to the death of the individual.

characteristic mode of spread. In addition, a tumor was needed which frequently is associated with the development of metastatic cutaneous and subcutaneous nodules which can be objectively evaluated by size and number as an index of tumor mass growth. Malignant melanoma fulfills these criteria and was chosen for study to determine if a correlation could be established between progression of disease by these parameters and the demonstration of circulating tumor cells. Studies in this laboratory have indicated that 20 per cent of the blood samples obtained from patients with melanoma contained tumor cells (6). A group of patients with malignant melanoma, clinically limited to the primary site or regional lymphatics, and undergoing surgery provided data about the relationship of circulating tumor cells to the subsequent clinical course.

METHOD AND MATERIALS

The technique for tumor cell isolation has been described previously by Malmgren and associates (7) and utilizes streptolysin-O and a millipore filter. Twenty cubic centimeters of heparinized blood are centrifuged, the plasma is removed, and the remaining cells are washed in isotonic saline. Lysis of red blood cells and polymorphonuclear leucocytes is accomplished by incubation with streptolysin-O, a hemolytic enzyme elaborated by streptococci. The resultant cell suspension of tumor cells and lymphocytes is filtered through a millipore filter of 5 micron pore size. The cells collected on the filter are fixed in Carnoy's solution and stained according to the Papanicolaou technique. Filters are screened at 150 magnification for cytologic evaluation. This method affords a quantitative recovery of circulating tumor cells in a given amount of blood.

The 42 patients included in this study were classified into two groups. One group contains 36 patients with disseminated malignant melanoma, most of whom were receiving chemotherapy. Serial peripheral blood samples were examined at a time when they underwent careful physical examination to determine progression of disease. Progression of disease was determined objectively by (1) repeated counts of cutaneous, subcutaneous, and lymph node metastases, (2) repeated measurements of individual tumors or metastases, and (3) the size and number of pulmonary metastases seen on roentgenograms of the chest. These methods constitute the most satisfactory means available for clinical assay of tumor mass growth of most types of metastatic neoplasms.

The other group contained 6 patients operated upon for clinically resectable malignant

melanoma. Preoperative peripheral blood samples and samples from regional veins draining the tumor area at the time of operation, as well as postoperative peripheral vein samples, were studied to correlate the finding of circulating tumor cells with the clinical course of the patient.

Lesions from all patients were histopathologically diagnosed as malignant melanoma. Twenty-eight of the 36 patients in the group with nonresectable disease have died at the time of this report. The patients who underwent operation for resectable disease have been followed up for recurrences or metastases and for circulating tumor cells.

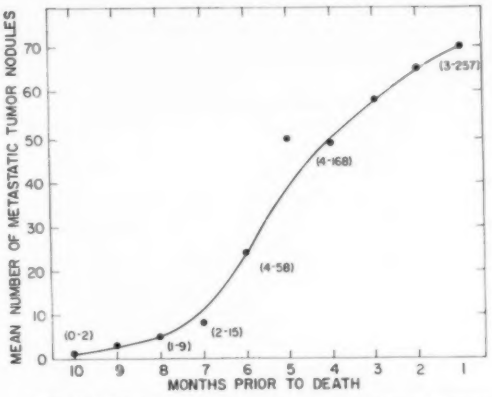


FIG. 3. This graph demonstrates progression of disease as determined collectively for 18 patients with advanced malignant melanoma as determined by objective tumor nodule count during a period 10 months prior to death.

RESULTS

Nonresectable malignant melanoma. Circulating tumor cells were identified in 18 per cent of 247 peripheral blood samples obtained from this group (Table I). Twenty-five of the 36 patients (70 per cent) with nonresectable malignant melanomas were found to have 1 or more blood samples containing malignant cells.

Relationship of circulating tumor cells to stage of disease. Twenty-eight of the 36 patients with nonresectable disease were observed until their deaths. The results of peripheral blood examinations during the 12 month periods prior to their deaths were tabulated. Initially, there was a low per cent of positive peripheral blood specimens, and terminally there was a sharp increase to 44.5 per cent in positive samples (Fig. 1).

The number of patients from whom blood samples were obtained during each month is shown in Figure 2. One to 3 samples from a patient were obtained within monthly intervals. Eight of 13 patients (62 per cent) were found to have circulating tumor cells during the final month of life.

The incidence of positive peripheral blood specimens is greater during the late stages of the patient's illness. However, circulating tumor cells are often found in peripheral blood sporadically many months before death. In 2 instances, circulating tumor cells were recovered when the disease appeared static. In one patient there was a slight decrease in number of skin metastases while in the other there was no clinical change.

Relationship of circulating tumor cells to progression of disease. Progression of disease was assayed by counts of cutaneous or subcutaneous metastatic nodules in 26 of 36 patients with malignant melanoma. Eighteen patients were studied at various intervals within the year before death. Progression of disease in this group is shown in Figure 3. The mean number of metastatic nodules increased from 1 to 71 during the 10 month interval prior to expiration. Individual patients were followed up from 3 to 9 months.

The data reveal a relationship between the rate of progression of disease as determined by objective criteria and the demonstration of melanoma cells in peripheral blood specimens. In patients with a slow increase in number of metastatic nodules or in the size of individual nodules, there were

TABLE I.—SUMMARY OF EXPERIENCES WITH PERIPHERAL CIRCULATING TUMOR CELLS IN PATIENTS WITH NONRESECTABLE MALIGNANT MELANOMA

	Total	*Positive*		*Suspicious*		*Negative*	
	No.	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Blood specimens studied	247	44	18	12	5	191	77
Patients studied	36	25	70	1	3	10	27

TABLE II.—RELATIONSHIP BETWEEN RATE OF DISEASE PROGRESSION AND PERIPHERAL CIRCULATING TUMOR CELLS IN PATIENTS WITH ADVANCED MALIGNANT MELANOMA

Per cent increase	*No. of positive blood specimens*	*No. of negative blood specimens*	*Per cent of specimens positive*
Number of metastatic tumor nodules per week (26 patients)			
0 to 10 per cent	6	49	11
10 to 20 per cent	3	16	16
20 per cent plus	6	17	26
	15	82	
Size of measurable lesions per week (5 patients)			
0 to 10 per cent	2	23	8
10 to 20 per cent	1	3	25
20 per cent plus	2	1	97
	5	27	

TABLE III.—SUMMARY OF EXPERIENCES WITH CIRCULATING TUMOR CELLS IN PATIENTS WITH RESECTABLE MALIGNANT MELANOMA

Case No.	*Preoperative peripheral blood specimens*		*Local blood specimens obtained at operation*		*Postoperative peripheral blood specimens*		*Clinical course*
	Positive	*Negative*	*Positive*	*Negative*	*Positive*	*Negative*	
1	1 (9 cells)	1		2		6	No evidence of recurrence 1 year after operation
2	2 (100 cells) (2 cells)	1		1		10	No evidence of recurrence 1 year after operation
3		3	1 (100 cells)	3	4 (4 cells) (4 cells) (3 cells) (2 cells)	25	Expired 12 months after operation with disseminated disease
4		3	1 (50 cells)	4	2 (1 cell) (46 cells)	6	Expired 3 months after operation with disseminated disease
5		6		2		8	No evidence of recurrence 3 months after operation
6		2		1	4 (100 cells) (11 cells) (2 cells) (7 cells)	4	No evidence of recurrence 9 months after operation
Total No.	3	16	2	13	10	59	
Per cent	16		13		14.5		

very few positive peripheral blood specimens. In contrast, positive blood specimens were more numerous in patients with rapid progression of disease. Occasionally, in a patient with slow progression of disease and negative peripheral blood specimens, there would be a rapid increase in tumor size concurrent with a positive blood sample. This course of events was demonstrated by a patient whose progress of disease was determined on the basis of measuring a metastatic axillary mass (Fig. 4). After his disease had slowly progressed for 4 months, the tumor rapidly enlarged during a 2 week period, after which its rate of enlargement was relatively slow again. Associated with this rapid increase in size of the axillary mass was the finding of peripheral circulating tumor cells.

A similar pattern is illustrated by a 36 year old woman whose progressive disease was demonstrated by metastatic skin nodules. Seven negative blood specimens were found, while the number of metastatic nodules gradually increased from 8 to 78 in 2 months. Then, in a single week the number of metastatic nodules rose from 78 to 156, during which time a positive peripheral blood specimen was obtained. The patient expired 5 months later.

To determine whether the association of rapid increase in rate of growth or appear-

ance of new metastatic nodules and the demonstration of circulating tumor cells was significant, the per cent increase in number of metastatic nodules was determined on a weekly basis for all patients from whom concurrent blood specimens were obtained (Table II). This value was determined by comparing the increase in number of tumor nodules per week to the previous week's observation. When the increase in number of tumor nodules was under 10 per cent per week, 11 per cent of the specimens evaluated were positive. This value increased to 26 per cent when the rate of progression in number of nodules was greater than 20 per cent per week.

In Table II, the second group shows the relationship between per cent increase in tumor size per week and the incidence of positive peripheral blood specimens in 5 patients with malignant melanoma. Blood specimens studied concurrently with an increase in size of less than 10 per cent per week were positive in 2 of 25 samples examined (8 per cent). More positive specimens were obtained when increase in size was greater than 20 per cent per week. In these two groups there is a correlation between the rate of disease progression and the finding of positive peripheral blood specimens.

Resectable malignant melanoma. Three of 19 preoperative peripheral blood specimens from 6 patients with surgically resectable malignant melanoma contained circulating tumor cells (Table III). These 3 specimens were obtained from 2 patients who failed to demonstrate circulating tumor cells in venous blood draining the region of the tumor at the time of operation. In both patients, prophylactic axillary dissections were performed; 2 of 13 lymph nodes from one patient contained tumor, and no tumor was found in 12 nodes from the other patient. In neither were the postoperative peripheral blood specimens positive, nor was there any clinical evidence of recurrent disease.

From 2 of the 6 patients a positive local blood specimen was obtained during operation. Recurrent disease developed in both within 8 months after operation, and they died with disseminated malignant melanoma.

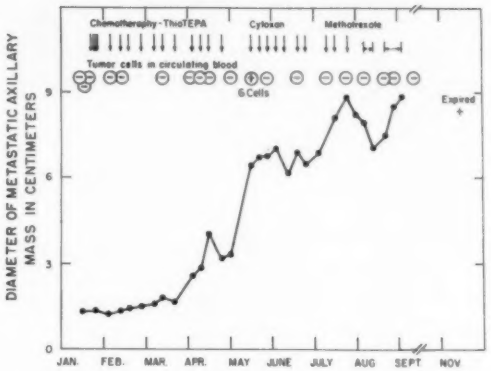


FIG. 4. Relationship between circulating tumor cells and disease progression in a patient with malignant melanoma. Note the finding of a positive specimen in relation to rapid rate of growth of the metastatic tumor.

One of these patients underwent a therapeutic radical groin dissection for recurrent disease (Case 3). Five of 18 nodes in the surgical specimen contained malignant melanoma. A sample of blood drawn from the femoral vein prior to operation contained numerous malignant cells (Fig. 6). Approximately 2 weeks after operation, a positive peripheral specimen was obtained. This was 8 months before the appearance of clinical or roentgenographic evidence of recurrent disease. The patient died with cerebral and pulmonary metastases approximately 1 year after operation.

DISCUSSION

The finding of circulating tumor cells in 70 per cent of a group of patients with disseminated melanoma is a higher incidence than has been reported in studies of patients with other advanced cancers. This observation may be attributed to processing a larger sample of blood, more efficient recovery, greater number of blood specimens obtained from each patient, a higher concentration of tumor cells in the peripheral blood of patients with melanoma, or a combination of these factors.

TABLE II.—RELATIONSHIP BETWEEN RATE OF DISEASE PROGRESSION AND PERIPHERAL CIRCULATING TUMOR CELLS IN PATIENTS WITH ADVANCED MALIGNANT MELANOMA

Per cent increase	*No. of positive blood specimens*	*No. of negative blood specimens*	*Per cent of specimens positive*
Number of metastatic tumor nodules per week (26 patients)			
0 to 10 per cent	6	49	11
10 to 20 per cent	3	16	16
20 per cent plus	6	17	26
	15	82	
Size of measurable lesions per week (5 patients)			
0 to 10 per cent	2	23	8
10 to 20 per cent	1	3	25
20 per cent plus	2	1	97
	5	27	

TABLE III.—SUMMARY OF EXPERIENCES WITH CIRCULATING TUMOR CELLS IN PATIENTS WITH RESECTABLE MALIGNANT MELANOMA

Case No.	*Preoperative peripheral blood specimens*		*Local blood specimens obtained at operation*		*Postoperative peripheral blood specimens*		*Clinical course*
	Positive	*Negative*	*Positive*	*Negative*	*Positive*	*Negative*	
1	1 (9 cells)	1		2		6	No evidence of recurrence 1 year after operation
2	2 (100 cells) (2 cells)	1		1		10	No evidence of recurrence 1 year after operation
3		3	1 (100 cells)	3	4 (4 cells) (4 cells) (3 cells) (2 cells)	25	Expired 12 months after operation with disseminated disease
4		3	1 (50 cells)	4	2 (1 cell) (46 cells)	6	Expired 3 months after operation with disseminated disease
5		6		2		8	No evidence of recurrence 3 months after operation
6		2		1	4 (100 cells) (11 cells) (2 cells) (7 cells)	4	No evidence of recurrence 9 months after operation
Total No.	3	16	2	13	10	59	
Per cent	16		13		14.5		

very few positive peripheral blood specimens. In contrast, positive blood specimens were more numerous in patients with rapid progression of disease. Occasionally, in a patient with slow progression of disease and negative peripheral blood specimens, there would be a rapid increase in tumor size concurrent with a positive blood sample. This course of events was demonstrated by a patient whose progress of disease was determined on the basis of measuring a metastatic axillary mass (Fig. 4). After his disease had slowly progressed for 4 months, the tumor rapidly enlarged during a 2 week period, after which its rate of enlargement was relatively slow again. Associated with this rapid increase in size of the axillary mass was the finding of peripheral circulating tumor cells.

A similar pattern is illustrated by a 36 year old woman whose progressive disease was demonstrated by metastatic skin nodules. Seven negative blood specimens were found, while the number of metastatic nodules gradually increased from 8 to 78 in 2 months. Then, in a single week the number of metastatic nodules rose from 78 to 156, during which time a positive peripheral blood specimen was obtained. The patient expired 5 months later.

To determine whether the association of rapid increase in rate of growth or appear-

ance of new metastatic nodules and the demonstration of circulating tumor cells was significant, the per cent increase in number of metastatic nodules was determined on a weekly basis for all patients from whom concurrent blood specimens were obtained (Table II). This value was determined by comparing the increase in number of tumor nodules per week to the previous week's observation. When the increase in number of tumor nodules was under 10 per cent per week, 11 per cent of the specimens evaluated were positive. This value increased to 26 per cent when the rate of progression in number of nodules was greater than 20 per cent per week.

In Table II, the second group shows the relationship between per cent increase in tumor size per week and the incidence of positive peripheral blood specimens in 5 patients with malignant melanoma. Blood specimens studied concurrently with an increase in size of less than 10 per cent per week were positive in 2 of 25 samples examined (8 per cent). More positive specimens were obtained when increase in size was greater than 20 per cent per week. In these two groups there is a correlation between the rate of disease progression and the finding of positive peripheral blood specimens.

Resectable malignant melanoma. Three of 19 preoperative peripheral blood specimens from 6 patients with surgically resectable malignant melanoma contained circulating tumor cells (Table III). These 3 specimens were obtained from 2 patients who failed to demonstrate circulating tumor cells in venous blood draining the region of the tumor at the time of operation. In both patients, prophylactic axillary dissections were performed; 2 of 13 lymph nodes from one patient contained tumor, and no tumor was found in 12 nodes from the other patient. In neither were the postoperative peripheral blood specimens positive, nor was there any clinical evidence of recurrent disease.

From 2 of the 6 patients a positive local blood specimen was obtained during operation. Recurrent disease developed in both within 8 months after operation, and they died with disseminated malignant melanoma.

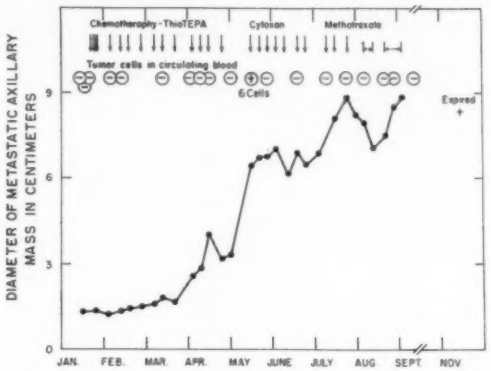


FIG. 4. Relationship between circulating tumor cells and disease progression in a patient with malignant melanoma. Note the finding of a positive specimen in relation to rapid rate of growth of the metastatic tumor.

One of these patients underwent a therapeutic radical groin dissection for recurrent disease (Case 3). Five of 18 nodes in the surgical specimen contained malignant melanoma. A sample of blood drawn from the femoral vein prior to operation contained numerous malignant cells (Fig. 6). Approximately 2 weeks after operation, a positive peripheral specimen was obtained. This was 8 months before the appearance of clinical or roentgenographic evidence of recurrent disease. The patient died with cerebral and pulmonary metastases approximately 1 year after operation.

DISCUSSION

The finding of circulating tumor cells in 70 per cent of a group of patients with disseminated melanoma is a higher incidence than has been reported in studies of patients with other advanced cancers. This observation may be attributed to processing a larger sample of blood, more efficient recovery, greater number of blood specimens obtained from each patient, a higher concentration of tumor cells in the peripheral blood of patients with melanoma, or a combination of these factors.

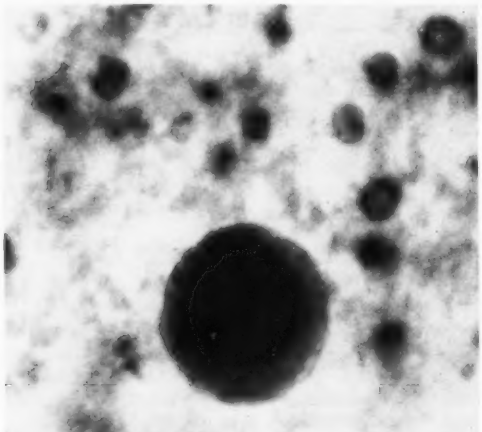


FIG. 5. Tumor cell with large nucleus and coarse chromatin pattern from a patient with malignant melanoma. Papanicolaou, ×1054.

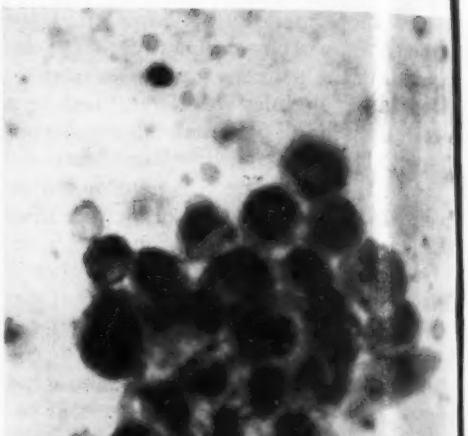


FIG. 6. Clump of tumor cells obtained from the femoral vein in Case 3 at operation. Note cellular size in comparison to lymphocyte in upper field. Papanicolaou, ×944.

This study supports the impression that circulating tumor cells are more often present in late stages of neoplastic disease. In spite of this relationship, sporadic positive samples have also been obtained from patients with early stages of malignant melanoma. Therefore, a negative or positive specimen is not by itself indicative of longevity. However, a positive peripheral sample is a generally unfavorable prognostic sign for the patient. Few attempts have been made to correlate the detection of circulating tumor cells with other factors. Engell noted that malignant cells in blood draining the tumor area were most closely related to histologic differentiation of the cancer (2). Positive cases were associated with decreased differentiation of the tumor.

The direct relationship between the per cent increase in the rate of tumor growth and the recovery of peripheral tumor cells is supported by individual patient studies as well as by an analysis of total experiences. Blood specimens were not studied at frequencies sufficient to determine whether the increased rate of tumor growth preceded or followed the occurrence of circulating tumor cells as shown in Figure 4. In 5 of 6 patients who demonstrated this relationship, the positive sample was obtained shortly after the observed increase in rate of tumor growth. In these cases, circulating tumor cells may have exfoliated from established metastases and not be the causative factor in the increased number of nodules or size of measurable lesions.

This study was not made to determine the effect of chemotherapy on malignant melanoma or on circulating tumor cells. However, in this series, in only 1 of 26 patients given chemotherapy was there demonstrated a measurable effect on the tumor. This patient received triethylenethiophosphoramide (thioTEPA).

The surgical group of patients presents an important series for study of circulating tumor cells in relation to metastases. Available evidence suggests that the host must destroy most circulating cancer cells. In animals the number of hepatic metastases has been shown to be proportional to the number of malignant cells injected into the portal vein. It is possible that a similar situation obtains in man and that the number of circulating cells at the time a primary tumor is removed may determine in part the fate of the patient. Fisher and Fisher think that cells in small numbers can actually remain "dormant" for extended periods and later manifest themselves in the form of metastases (4).

The relationship of circulating cancer cells to the prognosis of a patient with resectable disease cannot be concluded at this time. This experience with malignant melanoma would seem to indicate a poor prognosis if peripheral circulating tumor cells are found postoperatively in a surgical patient.

SUMMARY

1. Circulating tumor cells were found in 18 per cent of 247 peripheral blood specimens obtained from 36 patients with nonresectable malignant melanoma.

Twenty-five of 36 patients (70 per cent) studied in this category demonstrated tumor cells in 1 or more peripheral specimens.

2. A direct relationship was found between the rate of growth or appearance of new metastatic nodules and the finding of peripheral circulating tumor cells.

3. A greater frequency of positive specimens and patients with positive specimens was found in the late months of life.

4. Results of circulating tumor cell studies in 6 surgical patients are presented.

REFERENCES

1. Ashworth, T. R. A case of cancer in which cells similar to those in tumors were seen in the blood after death. Austral. M. J., 1869, 14: 146.
2. Engell, H. C. Cancer cells in the circulating blood. Acta chir. scand., 1955, 201: 1-70.
3. Idem. Cancer cells in the blood—a 5 to 9 year follow-up study. Ann. Surg., 1959, 149: 457-461.
4. Fisher, B., and Fisher, E. R. Experimental evidence in support of the dormant tumor cell. Science, 1959, 130: 918-919.
5. Fisher, E. R., and Turnbull, R. B., Jr. The cytological demonstration and significance of tumor cells in the mesenteric venous blood in patients with colorectal carcinoma. Surg. Gyn. Obst., 1955, 100: 102-108.
6. Malmgren, R. A., and Potter, J. F. Cancer cells in the circulating blood. South. M. J., 1959, 52: 1359-1362.
7. Malmgren, R. A., Pruitt, J. C., Delvecchio, P. R., and Potter, J. F. Method for cytological detection of tumor cells in whole blood. J. Nat. Cancer Inst., 1958, 20: 1203-1213.
8. Moore, G. E., Sandberg, A., and Schubarb, J. R. Clinical and experimental observations of the occurrence and fate of tumor cells in the blood stream. Ann. Surg., 1957, 146: 580-587.
9. Papanicolaou, C. N. Atlas of Exfoliative Cytology. Cambridge, Mass.: Harvard University Press, 1954.
10. Pool, E. H., and Dunlop, C. R. Cancer cells in the blood stream. Am. J. Cancer, 1934, 21: 99.
11. Quenzel, U. Zur Kenntniss des Vorkommens von Geschwulstzellen im zirkulierenden Blute. Upsala läk. fören. förh., 1921, 26: 1.
12. Roberts, S., Watne, A., McGrath, R., McGrew, E., and Cole, W. H. Technique and results of isolation of cancer cells from the circulating blood. Arch. Surg., 1958, 76: 334-346.
13. Thiersch, K. Der Epithelialkrebs, namentlich der Haut. Leipzig: 1865. Loc. cit. (2).

THE ABOLITION OF RENAL AUTOREGULATION BY RENAL DECAPSULATION

GUSTAVO BOUNOUS, M.D., MARIO ONNIS, M.D., and
HARRIS B SHUMACKER, JR., M.D., F.A.C.S., Indianapolis, Indiana

THE PHENOMENON of renal autoregulation seems well established. The mechanisms involved in this unique property of the kidney are poorly understood. Two challenging theories have been proposed. One suggests a physiologic automatic intrinsic vasoconstrictor response to increased arterial blood pressure provoked by some pressure-sensitive capacity of the kidney. This theory is based largely upon observations suggesting that cyanide and procaine may abolish autoregulation. Unexplained, however, are the facts that other sympathicolytic agents do not produce the same effect, that the volume of the kidney increases rather than decreases with rising arterial pressure, and that total surgical removal of the sympathetic nerve supply does not abolish autoregulation (1). A cell-separation theory of autoregulation has recently been advanced by Pappenheimer and Kinter according to which a change in resistance to higher blood pressures is brought about by increased viscosity or change in the distribution of the blood within the kidney. This theory, however, could not explain why some degree of autoregulation is observed during perfusion with fluids like dextran, containing no cells. Moreover, anesthetized dogs in which the hematocrit has been greatly reduced still show autoregulation.

These theories imply that active changes occur within the kidney at arterial pressures ranging from about 70 to 200 millimeters of mercury. It seems to us rather difficult to understand, from the viewpoint of the economy of the organism, why renal blood flow should normally be maintained throughout the lifetime at a definitely submaximal rate by some active process. We have wondered whether, instead, the kidney is anatomically constructed so that it receives near maximal, and perhaps optimal, blood flow at arterial pressures around 80 millimeters of mercury and only slightly greater blood flow at higher pressure ranges. The anatomy of the kidney is peculiar. Although a very small organ, it ordinarily has diverted through it almost one fourth of the total cardiac output, presumably because of low vascular resistance. At the same time, it is encased in a relatively nonexpansible fibrous capsule. It was the purpose of this investigation to learn whether renal decapsulation would abolish autoregulation.

Certain related studies seemed compatible with our premise. Intrarenal pressure, that is, the pressure within the renal capsule, has usually been found to be higher than in any other organ. Winton observed no effect of arterial pressure upon intrarenal pressure, and Gottshalk little. Montagnani and Swann and associates (18), however, and, more recently, Hinshaw and coworkers (7, 8) found that intrarenal pressure does, indeed, rise and fall with changes in perfusion pressure.

MATERIALS AND METHODS

In a control group of 10 dogs, renal blood flow and systemic blood pressure were measured during a 10 minute control period and at intervals after the rapid transfusion of 350 cubic centimeters of whole blood and 4

From the Department of Surgery, Indiana University School of Medicine, Indianapolis.

Aided by grants from the U. S. Public Health Service, the Indiana Heart Foundation, the James Whitcomb Riley Memorial Association, and by a contract between the Office of Naval Research, United States Navy, and Indiana University.

subsequent rapid transfusions of 100 cubic centimeters each. The same experiment was carried out in 10 dogs in which the renal capsules had been removed immediately beforehand. Decapsulation was performed in such a manner as to avoid grasping or handling the kidney. Traction on the anterior layer of perinephritic fat brought the kidney near the surface of the wound and the capsule was then incised and dissected off. The 5 or 10 small stellate veins which enter the capsule were carefully ligated with fine silk. In the rare instance during which the kidney was inadvertently damaged or blood loss occurred the animal was discarded. The blood used for transfusion was drawn from heparinized donor animals immediately prior to each experiment. It was slowly agitated before the transfusion in order to avoid sedimentation. Renal blood flow was measured directly by a technique previously described (2). Arterial blood pressure was determined with a U tube mercury manometer through a plastic catheter introduced into the infrarenal aorta through a femoral artery. Esophageal temperatures were observed with a telethermometer; temperatures remained constant throughout the experiments.

In 10 additional dogs, renal blood flow was measured before and during neurogenic hypertension produced by clamping both carotid arteries in the neck. The same study was carried out in 10 other dogs immediately after decapsulation of both kidneys.

In 5 dogs in which one kidney was previously decapsulated, renal arteriograms were obtained about 5 minutes after the rapid transfusion of 400 cubic centimeters of whole blood. A retrograde injection of 20 cubic centimeters of 50 per cent hypaque was made through a catheter introduced through the right femoral artery into the aorta and positioned so that its tip lay just above the renal arteries. Three films were made after the beginning of the injection at approximately 1 second time intervals. Renal interstitial pressures were recorded through a 23 gauge hypodermic needle filled with normal saline and introduced deeply into the renal tissue. It was connected by a plastic catheter to a mercury manometer or a strain gauge manometer recording on a polyvisocardiette.

In 5 control animals, in 5 subjected immediately beforehand to renal decapsulation, in 3 in which a complete bilateral thoracolumbar sympathectomy and splanchnicectomy has been performed approximately 10 days beforehand, and in 2 subjected to bilateral cervical section of the vagosympathetic trunk the phenomenon of autoregulation was studied in a different fashion. In these animals cannulations were performed for the usual direct gravity drainage method for measuring renal blood flow. In addition, a large plastic tube was introduced into the left atrium through a left thoracotomy. It was connected with tubing which was run through a small sigmamotor pump and was joined to another large plastic tube inserted into the aorta through a transverse arteriotomy above the point of origin of the inferior mesenteric artery. The 3 pairs of lumbar arteries arising between the level of the renal arteries and the insertion of the catheter were ligated. The catheter was fixed in place by two encircling heavy ligatures and the aorta was clamped above the origin of the renal arteries. The renal arteries were thus perfused with arterialized blood removed from the left atrium and delivered by means of the pump. A U tube manometer was connected with the aortic catheter close to the aorta. The pump was so regulated as to produce varying perfusion pressures ranging from 190 millimeters to 20 millimeters of mercury. Renal blood flow was measured at each perfusion level. The suprarenal aorta was never clamped until the perfusion was started, in order to avoid renal ischemia.

RESULTS

Transfusion of whole blood. The 20 healthy dogs studied varied in weight from 12.2 to 24 kilograms and averaged 16.1 kilograms.

TABLE I.—RENAL BLOOD FLOW IN CUBIC CENTIMETERS PER KILOGRAMS PER MINUTE AS RELATED TO RENAL ARTERIAL PRESSURE

Wt. of dog in kgm.	*Perfusion pressures in mm. Hg*								
	190	*170*	*140*	*120*	*100*	*80*	*60*	*40*	*20*
	CONTROL OBSERVATIONS								
13	17.5	19.5	19.2	20.2	19	16.6	16.6	11.5	8
17	15	15.4	15	15.1	14	10.3	10	7.6	2.8
15	13.6	14	15	14.6	15	11.3	8.7	4.7	3
12	16	16.6	16.6	16.6	17	14	10.3	5	1
12.8	17	18.3	18.5	16.6	15.5	14	11.8	9.5	5.4
Mean	15.8	16.8	16.9	16.6	16.1	13.2	11.4	7.6	4
	OBSERVATION WITH DECAPSULATED KIDNEYS								
16.8	19.2	16.3	14.2	13.3	12	11.1	10.7	8.6	4.4
12	33.3	28.3	26.5	24.5	20	18	17.2	13	5.9
16.4	31.2	24	23	18.3	12.6	12	11	8.4	4
15.7	26.2	18	15.1	14.8	13	12.2	9.5	8	1
13.6	24	20.3	18.3	16	12.2	11	7.8	6	1.5
Mean	26.8	21.4	19.4	17.3	13.9	12.9	11.2	8.8	3.3
	OBSERVATION AFTER BILATERAL VAGOTOMY								
12.8	16.1	19	20	20	19.8	18	10	6	4
14	13.6	13.6	14	14	14	10.2	8.6	6.9	3
Mean	14.8	16.3	17	17	16.9	14.1	9.3	6.4	3.5
	OBSERVATION WITH DENERVATED KIDNEYS								
18	29	22.2	26	23.1	23.1	21.3	18	12	2
12.4	29.4	27	27	26.9	24.2	20.4	17.2	15.5	0.5
17.5	24	22.5	22.5	23.1	23.1	18.3	17.2	10.1	2
Mean	27.4	23.9	25.1	24.3	23.4	20	17.4	12.5	1.5

The mean response of the normal dogs to massive blood transfusion is documented in Figure 1. The mean systolic blood pressure rose rapidly from about 140 millimeters of mercury to 167 millimeters of mercury and remained high throughout the experiment while a very small and almost certainly negligible increase in renal blood flow was noted. In 8 of the 10 the response was essentially the same as reflected by the mean values. However, the rise in blood pressure in them tended to be a little higher and there was less evidence of even questionable increase in renal flow. In 2 exceptional animals, both of which were very young, the renal capsule was apparently unusually expansile, gross enlargement of the kidney was observable after the transfusion, the blood pressure tended to remain at control levels, and the renal flow increased. An entirely different response from that observed in the 8 control animals mentioned and reflected in the mean values was noted when the same amount of blood was transfused into 10 decapsulated dogs. Here only a trivial initial average increase in blood pressure, from 131 to 140 millimeters of mercury, occurred after the 350 cubic centimeter blood transfusion. It returned quickly to control values and was not further altered by successive smaller transfusions. The renal blood flow, however, showed an immediate marked increase followed by further gradual increase, so that at the end of the period of observation it was 62 per cent above the mean control value. Each of these animals responded in precisely the same way, and the mean values accurately reflected the response in each. The kidneys all increased in size after the transfusion. Prior to the transfusion of blood the mean renal blood flow in the group of animals with decapsulation was 8 per cent above the average value of the control group while the systemic blood pressure was 8 per cent

TABLE II.—INFLUENCE OF BLOOD TRANSFUSION UPON RENAL INTERSTITIAL PRESSURE IN CONTROL AND IN DECAPSULATED KIDNEYS

No. of dog	*Before transfusion*		*After transfusion*	
	Control kidney	*Decaps. kidney*	*Control kidney*	*Decaps. kidney*
1	22	18	55	22
2	15	8	34	15
3	18	10	31	12
Mean	18.3	12	40	19

less than the average pressure in the control animals.

Renal blood flow studies with decreasing renal arterial pressure. In 10 decapsulated dogs weighing from 14 to 20 kilograms and averaging 16.5 kilograms, renal blood flow was measured at arterial pressures gradually reduced by means of a screwdown type Blalock clamp placed about the aorta above the renal arteries.

Although the mean values suggest autoregulation in those with renal decapsulation (Fig. 2), it was believed that the study was entirely unsatisfactory. These animals, in contrast with the controls, had low blood pressures at the onset, and observations of renal flow at higher pressure levels was possible in too few instances. We wondered whether one would find little evidence of autoregulation if the experimental animals could be studied at a higher pressure range. This presumption became evident when the phenomenon was studied by perfusion of the kidneys with arterialized blood (Table I and Fig. 3). When the perfusion pressure was decreased by increments from 190 to 20 millimeters of mercury, it was evident that the animals subjected to renal decapsulation showed no capacity at all for autoregulation. The drop in renal blood flow occurred progressively in an almost linear fashion with the drop in perfusion pressure. In contrast, there was practically no change in renal blood flow in the control animals, as the flow was somewhat less at 80 and then dropped as the pressure was lowered further in this group. These studies, then, demonstrated remarkable autoregulation in control animals and no autoregulation in those with renal decapsulation. They also showed clear-cut renal autoregulation both in animals previously subjected to bilateral thoracolumbar sympathectomy and splanchnicectomy and in animals with bilateral section of the cervical vagosympathetic trunks.

Renal blood flow in hypertension resulting from bilateral carotid artery occlusion. Ten control animals ranging in weight from 13.2 to 20 kilograms and averaging 15.7 kilograms

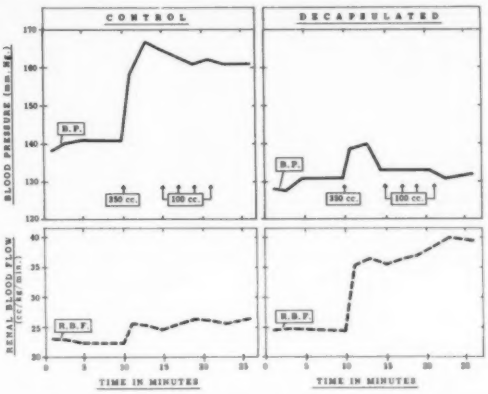


FIG. 1. Chart showing mean changes in blood pressure and renal blood flow occurring as a response to rapid transfusion of whole blood. The difference in response of control animals and of those with renal decapsulation is evident.

were studied before and after clamping of both carotid arteries in the neck. The same experiment was carried out in another group of 10 animals ranging in weight from 13 to 19.5 kilograms and averaging 15.9 kilograms in which both kidneys were decapsulated. Although some variations occurred in the level of blood pressure and of renal blood flow, each animal in both groups responded quite similarly. In both groups (Fig. 4) the mean systemic blood

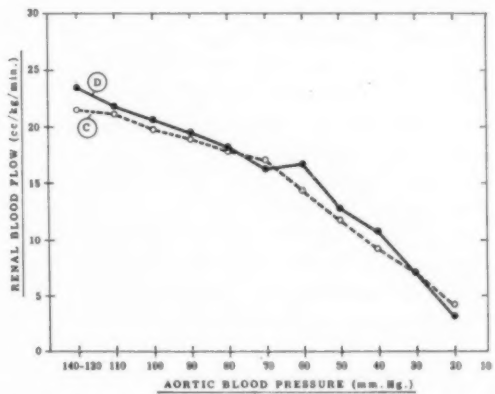


FIG. 2. Chart showing mean changes in renal blood flow as the aortic-renal artery pressure is reduced by suprarenal aortic clamping. *C*, Controls; *D*, denervated.

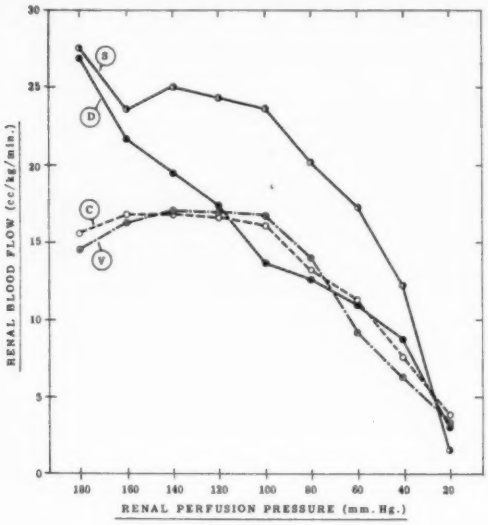


FIG. 3

FIG. 3. Chart showing autoregulation in: control animals, *C*, those with bilateral section of the cervical vagosympathetic chains in the neck, *V*, and those with renal denervation, *S*, but complete absence of autoregulation in animals with renal decapsulation, *D*.

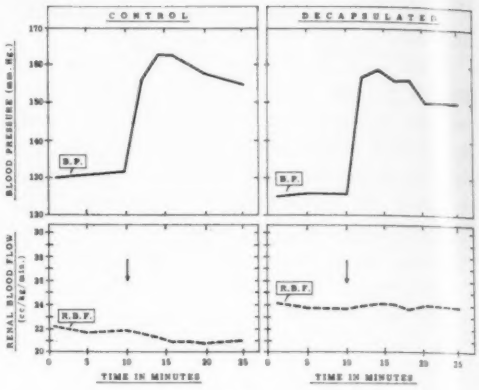


FIG. 4

FIG. 4. Chart showing similar responses of blood pressure and renal blood flow in normal dogs and in those with renal decapsulation as a response to hypertension resulting from clamping of both carotid arteries. Arrow indicates time of clamping of arteries.

pressure rose about 30 millimeters of mercury during the period of carotid artery occlusion. No significant changes were noted in renal blood flow.

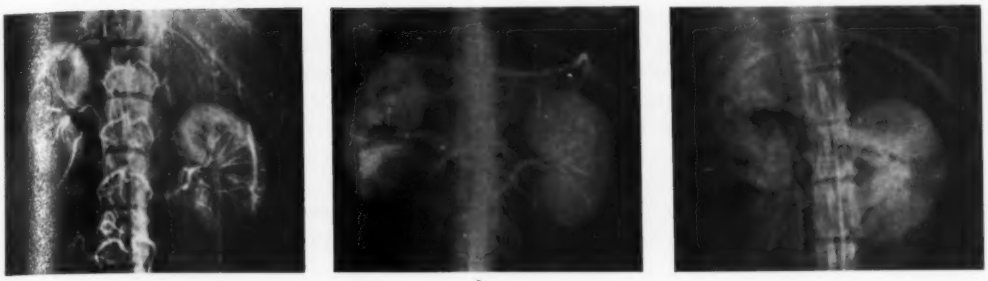
Renal interstitial pressure studies. In Table II the data are recorded concerning measurements of renal interstitial pressure before and during transfusion of 350 cubic centimeters of whole blood into 3 animals subjected to unilateral renal decapsulation. The intrarenal pressure in the normal kidney was found to average 18.3 millimeters of mercury while that in the decapsulated kidney averaged 12 millimeters of mercury. After rapid transfusion the intrarenal pressure rose to an average of 40 millimeters of mercury in the normal kidney. In contrast, the pressure in the decapsulated kidney rose on the average only to 19 millimeters of mercury, or almost precisely the pretransfusion value in the normal ones.

Arteriographic studies. The arteriographic studies carried out in animals with a unilateral renal decapsulation after the rapid transfusion of whole blood showed consistently that renal circulation was more rapid in the decapsulated kidney. The decapsulated kidney always increased in size in response to the transfusion.[1] The small branches of the renal artery appeared consistently larger and better opacified in the decapsulated kidney (Fig. 5a). Not infrequently the opaque medium had disappeared from the arterial tree of the decapsulated kidney, and the renal venous collecting system was filled at the same time that the arteriogram was evident in the normal kidney (Fig. 5b). Similarly, pyelographic visualization of the urinary collecting structures and the ureter occurred in the decapsulated kidney before any pyelogram was evident in the normal one (Fig. 5c).

DISCUSSION

The experiments described confirm again, with the in situ perfusion technique, the phenomenon of renal autoregulation in the normal dog as well as in dogs subjected

[1]Although the increase in size was always evident from direct observation, it was sometimes not apparent from the angiographic studies because of failure to have both kidneys in the same plane.



a b c

FIG. 5. Arteriographic studies in animals subjected to unilateral renal decapsulation and rapid transfusion of whole blood. The decapsulated kidney is on the right in a, on the left in b and c. Better filling of the small renal arterial branches, a, quicker venous filling, b, and more prompt pyelographic visualization, c, of the decapsulated kidney are shown.

to extensive thoracolumbar sympathectomy and splanchnicectomy and in animals with bilateral section of the vagosympathetic trunk in the neck (1). These experiments demonstrate conclusively that decapsulation abolished renal autoregulation. The transfusion of whole blood in normal dogs is attended by an increase in systemic arterial blood pressure and by no increase in renal blood flow. In contrast, animals with bilateral renal decapsulation have no significant increase in arterial blood pressure but a marked increase in renal blood flow. During such transfusions the intrarenal pressure of the normal kidney rises to levels over twice that of the control. In contrast, the intrarenal pressure in the decapsulated kidney rises during transfusion only to a level characteristic of the pretransfusion normal kidney. Direct observation of the decapsulated kidney and arteriographic studies demonstrate that during transfusion the decapsulated kidney increases visibly in size and has a faster circulation and a more rapid excretion of the contrast material. The experiments show the importance of interstitial renal pressure and its control to a large extent by the enveloping fibrous capsule in the phenomenon of autoregulation.

Studies reported in the literature reveal considerable controversy concerning intrarenal pressure and its possible influence on renal blood flow. Winton studied this matter indirectly by determining the ureteral pressure required to slow the flow of urine from the isolated perfused kidney. Using this method, he reported no appreciable change in intrarenal pressure when the blood pressure was varied from 80 to 180 millimeters of mercury. Miles and DeWardener studied intrarenal pressure directly with a saline filled needle, recording electronically. The renal pressure rose from 21 millimeters to about 50 millimeters of mercury during occlusion of the inferior vena cava. They did not report any significant difference in intrarenal pressure in normal and decapsulated kidneys either under normal circumstances or with elevated perfusion pressures. Selkurt and associates observed that the renal venous pressure rises from 7.5 to 22.4 millimeters of mercury upon partial venous obstruction. At the same time, renal blood flows determined directly and by clearance techniques decreased on the average about 15 per cent. They explained this decrease on the basis of a decrease in pressure gradient across the renal vascular circuit resulting from the increased venous tension. Semple and DeWardener found that increasing the venous pressure caused the kidney to become firm and elevated the intrarenal pressure. They assumed that increases in the venous pressure were transmitted to the outer surface of the walls of the intraparenchymal arteries or arterioles and that renal autoreg-

ulation was due to an active response of the muscular coats of the renal arteries and arterioles to changes in transmural pressure. Magnani and associates, during experimental obstruction of the inferior vena cava, observed a significant reduction of blood flow through the kidneys which was not observed in other vascular districts draining into the inferior vena cava. Haddy and associates suggested that the decreased renal blood flow observed during increased renal venous pressure was due to passive reduction in the caliber of the vessels through changes in transmural pressure resulting from stromal and possibly capsular rigidity and to active vasoconstriction. He found that the renal interstitial pressure rose almost equally with the rise in venous pressure. Gottschalk, measuring intrarenal pressure with a small hypodermic needle connected to a mercury manometer, found the dog's kidney to have an average value of 16 millimeters of mercury. Reducing the pressure in the renal artery by progressive compression of the abdominal aorta brought about no consistent change in interstitial pressure until the mean arterial pressure was lowered to approximately 40 millimeters of mercury. A constructive interpretation of the renal interstitial pressure as it relates to autoregulation was first suggested by Swann and associates (18). They found the intrarenal pressure to average 26 millimeters of mercury. They also observed that the intrarenal pressure was directly related to the renal perfusion pressure. During renal artery occlusion the interstitial pressure fell on the average from 26 to 11 millimeters of mercury. They believed that the elevation in intrarenal pressure with increasing blood pressure was related to the fact that the kidney was surrounded by a tough capsule. During the same year, Montagnani found a similar relationship between intrarenal pressure and pressure in the renal artery. He raised the pressure by blood transfusion and decreased the perfusion pressure by hemorrhage. A further interesting observation was made by Swann and Weaver (19). By measuring the dog's kidney with an oncometer they found that if the volume of the kidney without renal blood flow were taken to be 78 per cent, it increased to 100 per cent when the pressure was raised to 70 millimeters of mercury. Further increasing the blood pressure to 200 millimeters of mercury increased the volume of the kidney only to 110 per cent.

DeLangen observed a prompt decrease in intrarenal pressure almost to postmortem values when the renal capsule was incised. More recently, Hinshaw and associates (7, 8), in experiments on isolated perfusion of the dog's kidney, found that as the perfusion pressure was raised the associated rise in intrarenal pressure became greater within the pressure range where autoregulation was evident. They believed that renal interstitial pressure was regulated by a number of factors including the intrarenal vascular pressure, the relative inelasticity of the renal capsule, and stromal rigidity.

The suggestive evidence from the various studies recorded in the literature concerning the relationship of the renal capsule and of renal interstitial pressure to the phenomenon of renal autoregulation was clearly demonstrated in our own experiments. It must be assumed that renal interstitial pressure is partly maintained by the mechanical action of the enveloping fibrous capsule. The intrarenal blood pressure is in a sense counterbalanced by the intrarenal interstitial pressure. The kidney is a vascular organ. Winton estimated that 23 per cent of the kidney was vascular in structure. Approximately 20 per cent of the cardiac output is diverted through the kidneys. The kidney's peculiar anatomic structure, however, does not allow a proportional increase in blood flow as the arterial pressure is raised from approximately 80 to approximately 200 millimeters of mercury. The corresponding rise in intrarenal interstitial pressure counterbalances the increase in the pressure of the perfusing arterial blood. It must be assumed that the normal kidney has a near maximal

and perhaps near optimal blood flow with perfusion pressures of about 80 millimeters of mercury. As the perfusing pressure rises, little or no increase in renal blood flow occurs under normal circumstances. During a large transfusion of blood the normal dog's kidney undergoes no increase in renal flow and a significant rise in blood pressure occurs. In contrast, in the animal with renal decapsulation essentially no rise in blood pressure takes place and a significant increase in renal blood flow occurs. When the perfusion pressure is increased in the dog with renal decapsulation the renal blood flow increases proportionately.

In our studies it was found that 2 of the normal control animals did not respond to blood transfusion in a fashion similar to the other 8. They had less rise in blood pressure and some increase in renal blood flow and, therefore, responded somewhat like animals with renal decapsulation. It was interesting that in these 2 exceptional instances the animals were young, the renal capsules were apparently unusually distensible, and the kidneys visibly increased in size during transfusion just as occurs more dramatically in those with renal decapsulation. The role of the enveloping capsule and of interstitial renal pressure in regulating blood flow throws some interesting light upon the influence of complete renal denervation upon renal blood flow. In other studies (9) it has been shown that renal blood flow to the denervated kidney of the lightly anesthetized, well ventilated dog is slightly greater than its normally innervated control. The difference in flow between the two kidneys is exaggerated when the animal is made acutely hypovolemic by hemorrhage. Similarly, if the renal blood flow of the denervated animals is compared with that of normally innervated controls at various perfusion pressures, quite a difference is noted when the blood pressure in the renal arteries is in a low range and less difference when it is within a higher range (Fig. 6).[2] Apparently the denervated kidney receives a greater blood flow when the perfusion pressure is low enough so that the opposing factors of rising intrarenal pressure and encasing renal capsule are not significant.

[2]Constructed from data obtained in another study (2).

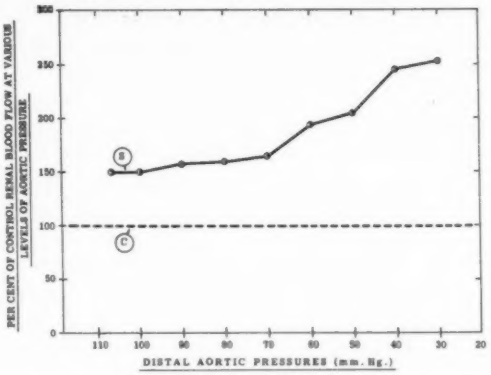


FIG. 6. Chart comparing renal blood flow in sympathetically denervated animals and controls at various levels of aortic pressure. *C*, Control animals; *S*, animals previously subjected to extensive bilateral sympathectomy and splanchnicectomy.

It is not surprising that no increase was found in renal blood flow either in normal animals or in those with renal decapsulation during the period of hypertension induced by clamping the carotid arteries in the neck. Kenney and Neil and Forster and Maes had also noted no increase in renal blood flow during such hypertension. Jourdan and Faucon believed that their experiments demonstrated that the entire visceral circulation was not appreciably affected by such neurogenic hypertension.

SUMMARY

The phenomenon of renal autoregulation can be abolished by renal decapsulation. It is dependent in large measure upon the normal presence of the relatively nonexpansile capsular envelope and the increasing intrarenal pressure as the blood pressure rises from approximately 80 millimeters of mercury to higher levels. A massive blood transfusion in the normal dog results in an increase in systemic arterial pressure and no increase in renal blood flow, whereas in animals with renal decapsulation a significant

increase in renal blood flow occurs with no significant increase in systemic arterial pressure. Perfusion studies in situ show that the phenomenon of autoregulation is clearly present in normal dogs, in sympathectomized and splanchnicectomized dogs, and in animals with a bilateral vagotomy. It is absent in animals with renal decapsulation. After massive blood transfusion, the interstitial renal pressure rises precipitously in the normal dog's kidney. In the decapsulated kidney it rises only to the pretransfusion level of the normal kidney. Angiographic studies demonstrate that after a massive transfusion the decapsulated kidney increases in size, has a faster renal blood flow, and excretes the contrast material more rapidly than does the normal kidney.

REFERENCES

1. Bounous, G., Onnis, M., Nash, F., and Shumacker, H. B, Jr. Renal autoregulation. Surg. Gyn. Obst., 1960, 111: 540.
2. Bounous, G., Shumacker, H. B, Jr., and King, H. Studies in renal blood flow—I, some general considerations. Ann. Surg., 1960, 151: 47.
3. DeLangen, C. D. Intrarenal pressure. Acta med. scand., 1957, 157: 279.
4. Forster, R. P., and Maes, J. P. Effect of experimental neurogenic hypertension on renal blood flow and GFR in intact denervated kidneys of unanesthetized rabbits with adrenal glands demedullated. Am. J. Physiol., 1947, 150: 534.
5. Gottschalk, G. W. A comparative study of renal interstitial pressure. Am. J. Physiol., 1952, 169: 180.
6. Haddy, F. J., Scott, J., and Fleishman, E. D. Effect of change in renal venous pressure upon renal vascular resistance, urine, and lymph flow rates. Am. J. Physiol., 1958, 195: 111.
7. Hinshaw, L. B., Ballin, H. M., Day, S. B., and Carlson, C. H. Tissue pressure and autoregulation in the dextran perfused kidney. Am. J. Physiol., 1959, 197: 853.
8. Hinshaw, L. B., Day, S. B., and Carlson, C. H. Tissue pressure as a causal factor in the autoregulation of blood flow in the isolated perfused kidney. Am. J. Physiol., 1959, 197: 309.
9. Jontz, Z., Shumacker, H. B, Jr., and Bounous, G. The influence of renal denervation upon renal blood flow. Surg. Gyn. Obst., 1960, 110: 622.
10. Jourdan, F., and Faucon, G. Participation respective des circulations peripherique et viscerale à la regulation tensionelle. J. physiol. path. gén., 1959, 51: 487.
11. Kenney, R. A., and Neil, E. Unpublished data. Correspondence from Heymans, C. Heymans, C., and Neil, E. Flexogenic Areas of the Cardiovascular System. Little Brown & Co., 1958.
12. Magnani, B., Bonomini, V., Campanacci, M., Sabattini, P., Biancani, G., and Pelliccioni, S. Equilibrio emodinamico intra ed extrarenale nell-ipertensione venosa sperimentale provocata. Fol. cardiol., 1958, 17: 355.
13. Miles, B. E., and DeWardener, H. E. Intrarenal pressure. J. Physiol., 1954, 123: 131.
14. Montagnani, C. A. Ricera sperimentale sulla pressione intrarenale. Sperimentale, 1952, 158: 102.
15. Pappenheimer, J. R., and Kinter, W. B. Hematocrit ratio of blood within mammalian kidney and its significance for renal hemodynamics. Am. J. Physiol., 1956, 185: 377.
16. Selkurt, E. W., Hall, P. E., and Spencer, M. P. Response of renal blood flow and clearance to graded partial obstruction of the renal vein. Am. J. Physiol., 1949, 157: 40.
17. Semple, S. J. G., and DeWardener, H. E. Effect of increased renal venous pressure on circulatory autoregulation of isolated dog's kidney. Circ. Res., 1959, 7: 643.
18. Swann, H. G., Moore, V., and Montgomery, A. V. The influence of arterial pressure on intrarenal pressure. Am. J. Physiol., 1952, 168: 637.
19. Swann, H. G., and Weaver, A. N. Relation of kidney volume to blood pressure. Fed. Proc., Balt., 1955, 14: 149.
20. Winton, F. R. Influence of changes in arterial pressure on intrarenal pressure in isolated mammalian kidney. J. Physiol., Lond., 1936, 87: 18.

AN ANALYSIS OF THE ROLE OF RADICAL SURGERY FOR GASTRIC CANCER

WALTER LAWRENCE, JR., M.D., F.A.C.S., and GORDON McNEER, M.D., F.A.C.S.,
New York, New York

HAS THE RECENT INCREASED USE of extended surgery for gastric cancer significantly affected the end results of treatment? In an attempt to answer this question, we compared our previous experience in the surgical treatment of gastric cancer with that of a recent period in which there was an enthusiastic application of extended techniques. The results of the various operations carried out within this recent period were also compared.

The therapeutic effectiveness of total gastrectomy or other extended procedures has been difficult to assess since application of these techniques in the past has been reserved for patients with advanced gastric cancer. Comparison of the end results of total gastrectomy with partial gastrectomy, for example, has almost always shown a lower salvage rate from the more radical procedure. This was definitely our finding in a previous study undertaken upon gastric cancer (1).

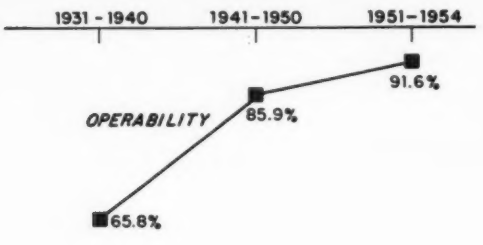
In view of the extent of the disease usually present in patients with gastric cancer for whom more radical techniques were chosen, a low salvage rate was not considered as an indictment of radical surgery. On the contrary, the occasional salvage of apparently hopeless patients by radical procedures, such as multiple organ resection, was one factor leading to the proposal that a more thorough operation be applied to favorable lesions. An extended operation was therefore designed on the basis of studies of the lymphatic drainage of the stomach and the expected sites of metastases to lymph nodes. A vigorous trial of this extended total gastrectomy (including an en bloc resection of both omenta, distal pancreas, and spleen) was initiated in 1951 in an attempt to improve our over-all results (3). Enough time has now elapsed to compare the end results of treatment of gastric cancer in this period of enthusiasm for "radical surgery" with the results achieved in a previous period on the same service when less extensive surgery was carried out. Operative procedures of varying extent within this current period have also been evaluated by comparing the results obtained with tumors of comparable location and pathology.

From the Gastric Service, Memorial Center, New York.

CLINICAL MATERIAL AND METHODS

The experience with gastric cancer on the Gastric Service of the Memorial Center, New York, during the years 1951 through 1954 was chosen for comparison with the results obtained during the 20 year period immediately preceding this. End results in the treatment of gastric cancer for the years 1931 through 1950 have been discussed in detail in another report (1). The results of specific operations within these two periods could not be compared in any meaningful fashion because of the changing criteria for selection of specific procedures. However, the over-all results during a period of extended surgery (1951 through 1954) could be compared with the end results for all patients obtained during the previous and more "conservative," period (1931 through 1950).

The classification and presentation of data from this study were essentially the same as reported previously. All patients submitted to operation were deemed "operable," and operative findings determined subsequent classification. The patients considered "resectable" were those in whom no gross tumor was left in situ at the end of the oper-



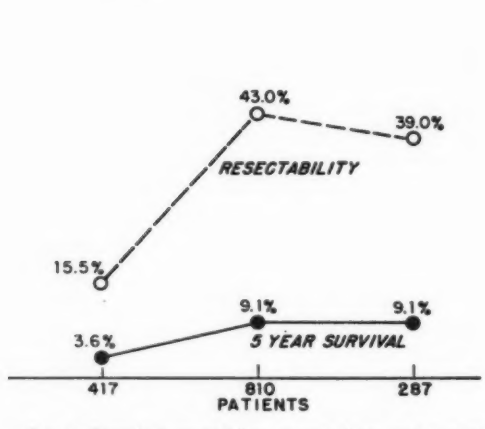


FIG. 1. Trends in operability, resectability, and 5 year survival in carcinoma of the stomach.

ative procedure. The 5 year survival statistics were expressed both as a proportion of all patients who survived definitive resection and as a percentage of all patients with gastric cancer seen during the chronologic periods considered.

In order to compare results of specific operations within the same time interval (1951 through 1954) the clinical material was separated in the following manner. The results obtained in all patients subjected to extended total gastrectomy in whom the primary tumor was limited to the distal part of the stomach or pars media were compared with the results obtained in other similar patients subjected to standard distal subtotal resection. Proximal subtotal resection (or cardiectomy) was compared with extended total gastrectomy in a similar fashion for lesions of the proximal third of the stomach. The presence or absence of lymphatic metastases was carefully tabulated for each group. For purposes of the comparison of the therapeutic effectiveness of subtotal and extended total gastrectomy, tumors extensive enough to require total gastrectomy were not included in this specific analysis.

RESULTS

In the years 1951 through 1954, 287 patients with adenocarcinoma of the stomach were seen. Of these, 263 patients were operable (91.6 per cent), 112 were subjected to curative resection (39 per cent), and 26 patients lived 5 or more years without evidence of metastases or local recurrence (9.1 per cent). These findings are compared with those of the 20 year period immediately prior to this in Figure 1. Although there was an improvement noted in the over-all 5 year survival between the first and second decades of the 20 year study, there was no further improvement in this figure in the most recent period.

Results of curative resection. The 5 year survival rate of the 112 patients subjected to curative resection between 1951 and 1954 was 23.2 per cent for all patients, and 26.8 per cent for those patients surviving the operation. The comparable 5 year survival rates for the years 1931 through 1950 were almost identical (21.6 per cent and 27 per cent respectively). These were the over-all results obtained despite a marked increase in application of total and extended total gastrectomy during the period 1951 through 1954 (Fig. 2).

The results of treatment after extended total gastrectomy in 52 patients were then compared with the results of proximal or distal subtotal gastrectomy in 51 patients during the period 1951 through 1954. Even though operative mortality was eliminated from the statistical comparison, subtotal gastrectomy was associated with a higher 5 year survival rate (35.4 per cent) than extended total gastrectomy (21.4 per cent). This comparison is quite misleading, however, since the incidence of lymphatic metastases in the group subjected to subtotal

gastrectomy was only 58.3 per cent, as compared with 83.3 per cent for those treated by extended total gastrectomy. If only the patients with metastases to lymph nodes are considered, the 5 year survival rate after extended total gastrectomy (17.1 per cent) was actually slightly higher than after proximal or distal subtotal gastrectomy (14.3 per cent). Although this difference is probably not significant in the statistical sense (Table I), there are living today patients whose disease could not have been completely resected by any procedure which did not encompass metastases found in the pancreatolienal nodes.

Comparison of subtotal gastrectomy with extended total gastrectomy for similar lesions. The comparison of results of the specific procedures shown may not give a clear picture of the potential value of these operations. This is due to the fact that the standard subtotal gastrectomy (proximal or distal) cannot be utilized in every patient, particularly if there is an anatomically advanced lesion. To determine the comparative effectiveness of extended total gastrectomy and subtotal gastrectomy, selection of patients was carried out as outlined previously. This smaller group within the series of cases treated by extended total gastrectomy represented those patients in whom the surgeon elected to carry out a more extensive operative procedure, even though it would have been technically possible to perform a subtotal gastric resection. The factor of operative mortality was eliminated from this comparative study as our interest was in the curative potential of extended total gastrectomy as compared to standard subtotal resection for comparable lesions.

Analysis of the results of treatment of those lesions technically suitable for distal subtotal gastrectomy is shown in Table II. If the factor of lymphatic metastases were not taken into consideration, there was no apparent difference in the 5 year survival of patients managed by either operation. When metastases were present in lymph nodes there was actually a marked difference in 5

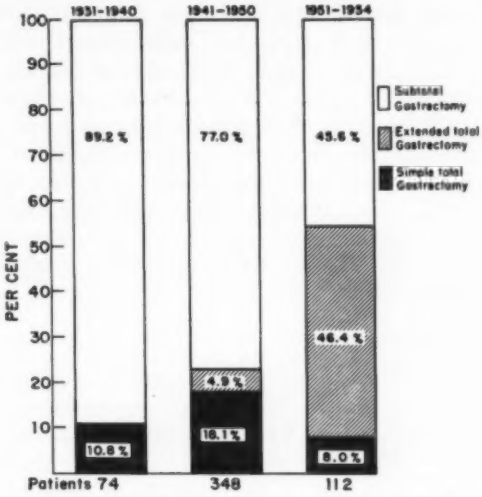


FIG. 2. Trends in choice of curative resection method for carcinoma of the stomach.

year survival, although the number of patients in this analysis is admittedly small. Only 4 patients of 23 with lymphatic metastases who were subjected to subtotal resection (17.4 per cent) survived 5 years. In a group of 12 patients with these same anatomic and pathologic findings who were subjected to extended total gastrectomy, there were 4 patients (33.3 per cent) who lived 5 or more years without evidence of disease.

Those lesions resected by extended total gastrectomy, though anatomically suitable for proximal subtotal resection of the stomach, were then examined. Of 21 patients with such lesions, only 3 were salvaged, 2 of whom had metastases to lymph nodes. In this same period, only 1 of 7 patients treated by proximal subtotal gastrectomy was clinically cured. All those with lymphatic metastases died of cancer.

Operative mortality. The factor of immediate mortality resulting from operation has been eliminated from most of the comparisons in an attempt to estimate the curative potentialities of the technique of extended total gastrectomy as compared with the more conservative resectional procedures. As one

might expect, the operative mortality was greater after extended total gastrectomy (19.2 per cent) than after subtotal gastrectomy (5.9 per cent) during the 4 year period 1951 through 1954. During the last 2 years of this study, however, there was significant improvement in these figures as shown in Table III. Complications and operative mortality after extended total gastrectomy have been discussed in detail in another report (2).

DISCUSSION

The therapeutic effectiveness of extended total gastrectomy in the management of gastric cancer has been difficult to evaluate. This procedure accomplishes a more thorough resection of the "lymphatic bed" of the stomach by virtue of removing the pancreatolienal nodes. This fact and the established significance of lymphatic metastases in the prognosis of this disease are what led many surgeons, including ourselves, to advocate the increased use of extended operations.

Although studies of lymphatic spread of gastric cancer gave credence to the concept of more radical surgery for this disease, it must be admitted that there have been some undesirable sequelae. The operative mortality, despite improvement, is greater than with subtotal gastrectomy at this time. Postgastrectomy nutritional difficulties and symptoms have been more common after total gastrectomy than subtotal resection, although these problems have often been very exaggerated. It has even been suggested by Rush and associates that late mortality after total gastrectomy in an appreciable number of cases is due solely to causes related to the anatomic and nutritional defect produced by this operation. Although this has not been our own experience, it seemed desirable to attempt to make an analysis of our results obtained with standard subtotal resection and extended surgery for comparative purposes.

A marked increase in performance of extended surgery for gastric cancer in the years 1951 through 1954 supplied a large enough series for comparison with our previous experience during years in which conservative techniques were more frequently used. From the practical standpoint, the over-all results obtained showed no really significant improvement, although definite advantage had been expected from this logical extension of our surgical approach. The validity of this disappointing finding in the over-all survival rate was confirmed by the observation that 5 year survival in the two periods was identical when only operative survivors of curative resection were considered.

Despite these discouraging findings a more detailed comparison was made of subtotal gastrectomy and extended total gastrectomy within this recent period. In a small group of extensive lesions in which total resection was required, due to anatomic extent of the primary lesion, the result after extended total gastrectomy was invariably unsuccessful. In our previous analysis of the results of simple total gastrectomy the 5 year survival rate was only 10 per cent. In most instances, those patients had a complete gastrectomy of necessity and were comparable to this group. A large proportion of the patients in whom extended total gastrectomy was utilized had primary lesions involving the proximal portion of the stomach. Unfortunately, the survival rate of patients with tumors in this location has been unusually poor in our series by both the conservative and radical techniques of resection. It was of interest, however, that 2 patients with proximal lesions and lymphatic metastases were successfully treated by extended total gastrectomy. One of these patients actually had metastases in the pancreatolienal nodes. There were no patients with lymphatic metastases salvaged by proximal subtotal gastrectomy during the period of investigation from 1951 through 1954.

A smaller number of patients subjected to extended total gastrectomy had tumors comparable to those for which distal subtotal gastrectomy was utilized. When those pa-

TABLE I.—COMPARISON OF RESULTS AFTER SUBTOTAL GASTRECTOMY AND EXTENDED TOTAL GASTRECTOMY (1951–1954)

	Subtotal gastrectomy				Extended total gastrectomy			
			5 year survival				5 year survival	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
All patients	51				52			
Survivors of operation	48	100	17	35.4	42	100	9	21.4
Nodes positive	28	57.3	4	14.3	35	83.3	6	17.1
Nodes negative	20	42.7	13	65.0	7	16.7	3	42.9

TABLE II.—COMPARISON OF RESULTS AFTER SUBTOTAL GASTRECTOMY AND EXTENDED TOTAL GASTRECTOMY (1951–1954)

	Subtotal gastrectomy				Extended total gastrectomy			
			5 year survival				5 year survival	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Patients with lesions of distal stomach and pars media	43				19			
Survivors of operation	41	100	16	39	15	100	6	40
Nodes positive	23	56.1	4	17.4	12	80	4	33.3
Nodes negative	18	45.9	12	66.7	4	20	2	66.7

TABLE III.—OPERATIVE MORTALITY AFTER DEFINITIVE RESECTION FOR CARCINOMA OF THE STOMACH

	1951–1954			1953–1954		
	No. of patients	Surgical deaths		No. of patients	Surgical deaths	
		No.	Per cent		No.	Per cent
All patients	112	15	13.4	49	3	6.1
Subtotal gastrectomy	51	3	5.9	25	—	—
Proximal	8	1	12.5	4	—	—
Distal	43	2	4.7	21	—	—
Simple total gastrectomy	9	2	22.2	1	—	—
Extended total gastrectomy	52	10	19.2	23	3	13

tients with lymphatic metastases were subjected to scrutiny, there was a strong suggestion of improvement in survival rate as a result of the extended operation. Again, the actual number of patients demonstrating this advantage was too small to affect the overall results significantly. There was another patient in this particular group, now living and well 8 years after resection was performed who had metastases to the pancreatolienal nodes.

It is apparent that increased application of extended surgery has not significantly improved the outlook of the average patient with gastric cancer. For this reason it is not our present policy to subject all patients with this disease to extended total gastrectomy. On the other hand, there are patients who may be successfully treated by the extended operation, but not by subtotal resection. The problem is to know just exactly when to apply the extended operation.

For proximal gastric lesions we believe that proximal subtotal gastrectomy has no advantage over the extended technique. Increased morbidity, mortality, and subsequent dietary difficulties occur with both operations but a more effective lymphatic dissection is accomplished by the extended technique. Therefore the extended total gastrectomy is used if the patient has no medical contraindications and no distant spread of tumor, and proximal subtotal gastrectomy is employed as a palliative procedure. With lesions of the distal one-third of the stomach, distal subtotal gastrectomy is performed if there is an adequate gross margin between the borders of the lesion and the line of resection. With larger lesions, of the pars media, or with evidence of adjacent nodal metastasis, the extended total gastrectomy is usually carried out in view of the suggestive evidence of advantage from this operation with this particular clinical setting.

CONCLUSIONS

The results of this study suggest that extended surgical techniques for the treatment

of gastric cancer should be applied on the basis of the pathologic conditions found at operation rather than in a routine manner for all patients with this disease. It also seems unlikely that more extensive procedures will produce any major improvement in the end results of gastric cancer.

REFERENCES

1. McNeer, G., Lawrence, W., Jr., Ashley, M. P., and Pack, G. T. A report upon the end results in the treatment of gastric cancer. Surgery, 1958, 43: 879-897.
2. McNeer, G., Lawrence, W., Jr., Ortega, L. G., and Sunderland, D. A. A study of early results of extended total gastrectomy for cancer. Cancer, 1956, 9: 1153-1159.
3. McNeer, G., Sunderland, D. A., McInnes, G., Vandenberg, H. J., and Lawrence, W., Jr. A more thorough operation for gastric cancer. Cancer, 1951, 4: 957-967.
4. Rush, B. F., Brown, M. W., and Ravitch, M. M. Total gastrectomy; an evaluation of this procedure in the treatment of gastric cancer. Cancer, 1960, 13: 643.

OBSERVATIONS ON THE ROLE OF THE LIVER IN HYDROCORTISONE METABOLISM

RICHARD W. STEENBURG, M.D., LOUIS L. SMITH, M.D.,
WILLIAM C. SHOEMAKER, M.D., and FRANCIS D. MOORE, M.D., F.A.C.S.,
Boston, Massachusetts

THE ENDOCRINE ENVIRONMENT of the injured organism is, in part at least, determined by an increased rate of production of the adrenal steroid hormones. Evidence has gradually accumulated that there occurs in association with this increased adrenal production of hormone, a distinct alteration in the rate at which these steroids are metabolized, excreted, or inactivated. The net effect of this decreased rate of disposal is an increased concentration of hormone available to the tissues and, potentially, an enhanced biologic effect from a given amount of hormone secreted.

In the adrenalectomized rat on constant steroid maintenance, increased urinary nitrogen excretion was observed following fracture. This metabolic change, coincident with trauma, was not seen in similar animals who had received no cortical steroid. From these studies, Ingle and associates reasoned that metabolic change in this instance did not require an altered steroidal environment but only the presence of steroid hormone. Thus adrenal cortical hormone "permitted" the metabolic response but did not "initiate" it. These results might alternatively be interpreted as representing a manifestation of the delay in cortical hormone destruction and/or excretion following trauma, and hence a "cortical effect" despite constant dose. The evidence for this latter interpretation has been strengthened by the use of quantitative microtechniques for the measurement of biologically active steroid hormones in plasma.

Lefemine, Sandberg, and Steenberg and their respective associates have noted in patients, after operations, the occurrence of blood levels of free 17-hydroxycorticosteroids exceeding those observed in the normal patient following maximum effective infusions of ACTH. Similarly, Steenburg and associates found that this ACTH infusion, when administered in the postoperative period, produced a significantly higher level of 17-hydroxycorticosteroids than did the same stimulus preoperatively. Murray and Sandberg and their respective associates confirmed these observations by the administration of hydrocortisone to normal and postoperative patients. It was found that the disappearance of infused steroid was often delayed in the postoperative state. Finally, in the adrenalectomized dog given a standard infusion of hydrocortisone, greater blood levels of free hormone were observed after anesthesia and operation than when the animal was awake and immobilized. The endocrine environment following trauma, then, is determined by a summation of the increased production of adrenal steroid hormones and a decrease in the organism's rate of metabolism or excretion of these substances. The nature and cause of this metabolic alteration, however, is not clear.

A decrease in the disappearance rate of injected hydrocortisone has been observed in association with cirrhosis of the liver in

From the Department of Surgery, Harvard Medical School, Peter Bent Brigham Hospital, Boston.
This work was aided by the Atomic Energy Commission through a contract (AT (30-1) -733) with the Peter Bent Brigham Hospital, and by the Subcommittee on Metabolism in Trauma, Advisory Committee on Metabolism, Office of the Surgeon General, United States Army, through a contract (DA-49-007-MD-472) with Harvard University, and by a grant (A-2657) from the National Institutes of Health, United States Public Health Service. Assistance was also received from the Winthrop Laboratories, Inc.

man by Brown and associates. Similarly, a distinct delay in the rate of metabolism of steroid hormones has been documented by Miller and Axelrod in the isolated perfused cirrhotic rat liver. Transient hepatic dysfunction has been thought by Schmidt and associates to occur after injury, suggesting an association between the delay in steroid metabolism in the cirrhotic and in the postoperative patient. Indeed, in patients, the postoperative delay in steroid metabolism has been correlated with abnormal retention of injected bromsulphalein.

On the other hand, severe hepatic dysfunction is a rarity in clinical surgery aside from those instances of existing liver disease. Morphologic changes of unknown consequence have been described by Cole and Leuchtenberger in the liver following trauma. Similarly, biochemical aberrations after injury, attributed to hepatic dysfunction, have been recorded by Beecher and associates and Scott and associates. In general, however, the liver continues to function effectively, even after severe injuries. There are reasons to doubt that hepatic dysfunction per se should be held responsible for the rather impressive changes in 17-hydroxycorticosteroid metabolism which follow even relatively simple and uncomplicated surgical procedures.

The capacity of the liver to metabolize cortical steroid hormone has been demonstrated in several experimental preparations. The perfused rat liver has been shown by Hechter and associates (9) to metabolize corticosterone at the rate of 100 micrograms per minute per gram of liver, at a perfusate level of 10 milligrams per cent. Transferred to a liver the size of the human liver, this rate would represent the destruction of 15 grams of hormone per hour. This figure is more impressive when one considers the fact that the maximum secretory capacity of the human adrenal probably never exceeds 15 milligrams per hour (a thousandfold difference). Further, in the dog studied immediately after operation, with infusion of hydrocortisone into the portal vein at a rate of 1,230 micrograms per minute, Hechter and associates found that only 20 per cent of the infused steroid appeared in the hepatic vein. Since hepatic tissue levels of steroid did not rise concomitantly, it was estimated that the liver "transformed" this infused hydrocortisone at a rate of 490 micrograms per minute. This represents a rate of metabolism which exceeds, by a factor of at least 20, the maximum adrenal output of the intact dog. Ganong and associates observed this rate in an animal which had only just responded from anesthesia after a major surgical procedure. The great capacity of the liver for steroid metabolism is well established. It seems improbable, therefore, that alterations in hepatocellular function, as demonstrated only by minor increases in bromsulphalein retention, could result in a diminished disappearance rate of hydrocortisone from the general circulation.

It was our purpose in these experiments to study hepatic transformation of infused hydrocortisone in adrenalectomized dogs maintained in a state as close to normal as possible. Further, we hoped to evaluate the effect of increasing portal venous blood concentrations of this hormone without altering the rate at which steroid was infused by introducing the hormone directly into the portal vein. Finally, attempt was made to determine the effect of an operation on these functions of steroid metabolism.

MATERIAL AND METHODS

Animal preparation. Adult mongrel dogs, weighing 20.4 to 31 kilograms, were selected for study. The spleen was removed through a midline abdominal incision under light pentobarbital anesthesia. A polyethylene cannula was inserted into the main left hepatic vein by the method previously described from these laboratories (21). Similar sampling catheters were introduced through the splenic vein into the portal vein, and in 5 instances, into the remnant of the splenic artery. The catheters were brought out through lateral abdominal stab wounds and fixed to the skin. Subsequently, both adrenals were removed and the abdomen closed.

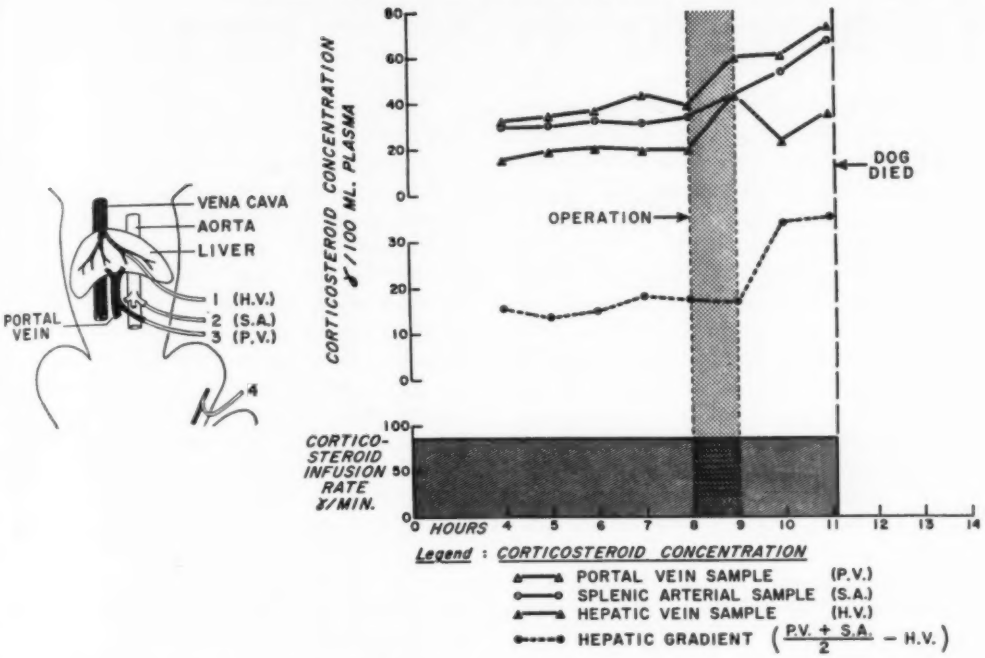


FIG. 1. Effect of operation on portal venous, hepatic venous, and splenic arterial corticosteroid concentrations in dog 7. Constant hydrocortisone infusion via a limb vein (*4*) of the adrenalectomized dog resulted in stable plasma concentrations of 17-hydroxycorticosteroids in blood from splenic artery (*SA, 2*) portal vein (*PV, 3*) and hepatic vein (*HV, 1*). After 8 hours, the animal was operated upon. There was a subsequent rise in plasma concentrations of steroids in samples from all sources. The hepatic steroid gradient $\left(\frac{(PV)+(SA)}{2}-(HV)\right)$ similarly increased.

The animal was then allowed to recover. Each was maintained on intravenous hydrocortisone (20 milligrams every 8 hours), the last dose being administered 16 hours prior to the experimental "run." Routine kennel rations and water were allowed ad libitum. Heparin solution was administered through the sampling cannulas every 8 hours following the operation; the total dose approximated 3.0 to 4.5 milligrams per kilogram per day. Penicillin was administered routinely.

Experimental protocol. By the third postoperative day the animals had fully recovered. They were alert, afebrile, and active. At this time each was placed in a Pavlov stand in which he rested quietly in a standing position. A constant infusion of hydrocortisone was administered through a fine polyethylene catheter placed in a limb vein. The hydrocortisone dose was calculated to approximate 5 milligrams per kilogram per 24 hours, except in dog No. 10 in which it was 2.5 milligrams per kilogram. The hydrocortisone was diluted in normal saline and delivered at a constant rate approximating 50 cubic centimeters per hour. The actual steroid infusion rate for each animal was subsequently calculated from quadruplicate steroid analysis of the infusate and the observed volume delivered.

Twenty milliliters of blood were aspirated from each of the 2 or 3 sampling catheters at the beginning of the experiment. Again 4 hours after the beginning of the infusion, and hourly thereafter, similar samples were withdrawn. Blood samples, obtained in heparinized syringes, were centrifuged as

TABLE I.—THE EFFECT OF OPERATION ON PORTAL VENOUS (PV), HEPATIC VENOUS (HV), AND SPLENIC ARTERIAL (SA) CORTICOSTEROID CONCENTRATIONS

Dog No. Weight, kgm. Sex	Infusion rate, mcgm./min.	Sample	17-hydroxycorticosteroids, mcgm. per cent													
			Hours						Preop. mean	Hours						Postop. mean
			0	4	4	6	7	8*		9†	10	11	12	13	14	
1		PV	0	25.9	—	32.6	34.0	37.8	32.6	46.7	39.5	33.5	34.4	36.5	31.0	36.9
28.7 F	112.3	HV	—	19.5	—	21.6	22.0	29.2	23.1	27.4	23.9	25.5	25.4	29.8	27.4	26.6
4		PV	0	12.1	17.1	17.7	16.7	18.8	16.5	25.4	17.6	18.4	19.4	24.8	20.9	21.1
25.4 F	73.3	HV	0	7.7	6.7	12.6	10.9	11.9	10.0	9.7	12.2	11.9	10.8	17.7	12.1	12.4
5		PV	1.3	—	22.3	24.3	—	23.1	23.2	28.1	26.5	28.4	24.6	—	25.6	26.6
21.5 M	66.9	SA	0	22.4	27.4	22.8	22.1	—	23.7	26.1	24.1	23.5	30.8	24.6	27.4	26.1
		HV	1.8	10.9	16.1	18.5	12.9	13.0	11.9	17.5	16.3	20.6	17.1	23.4	23.5	19.7
7		PV	—	31.7	34.0	36.6	44.1	38.5	37.0	60.0	60.2	73.3	—	—	—	64.5
26 M	84.5	SA	0	29.1	29.5	34.0	30.9	33.3	31.4	42.9	52.6	66.3	—	—	—	53.9
		HV	—	14.5	17.9	20.3	19.4	18.6	18.1	42.4	22.2	34.4	—	—	—	33.0
9		PV	0	15.5	15.3	16.7	11.5	13.9	14.6	22.2	16.0	16.4	19.8	11.7	24.3	18.4
31 M	78.6	SA	—	11.6	14.6	13.0	13.3	16.7	13.8	15.7	14.3	16.2	14.8	18.3	21.4	16.8
		HV	0	2.4	7.8	—	7.7	5.2	5.8	10.7	16.7	11.3	12.0	7.6	9.8	11.4

*Beginning of operation.
†End of operation.
Constant hydrocortisone infusion was administered through a peripheral vein for the duration of the experiment. The 1 hour exploratory laparotomy was performed after 8 hours. Plasma concentrations of free 17-hydroxycorticosteroids were measured in samples from portal vein, hepatic vein, and in 3 instances from the splenic artery, at hourly intervals. Results are expressed in micrograms per cent plasma.

TABLE II.—EFFECT OF INCREASING PORTAL VEIN CONCENTRATIONS OF CORTICOSTEROID

Dog No. Weight, kgm. Sex	Infusion rate mcgm./min.	Sample	17-hydroxycorticosteroids, mcgm. per cent													
			Hours						Pre-switch mean	Hours						Post-switch mean
			0	4	5	6	7	8		9	10	11	12	13	14	
3		PV	0	24.3	—	20.0	21.2	22.4	22.0	—	—	—	—	—	—	—
21.4 M	70.8	SA	0	19.4	—	18.9	18.7	21.3	19.6	14.0	—	13.0	10.3	13.8	—	12.8
		HV	0	11.8	—	5.5	9.4	8.6	8.8	15.2	11.7	14.3	11.1	15.7	—	13.6
10		PV	0	8.9	5.4	5.4	8.6	7.4	7.1	—	—	—	—	—	—	—
29 M	48.8	SA	0	6.7	5.3	5.4	7.3	9.5	6.8	3.6	7.0	5.6	8.7	8.2	12.7	7.6
		HV	0	4.4	2.3	4.8	3.3	3.8	3.7	5.4	5.7	5.9	8.8	11.2	12.6	8.3

Concentrations of free plasma 17-hydroxycorticosteroids (in micrograms per cent) in plasma, from portal vein (PV), splenic artery (SA), and hepatic vein (HV) during peripheral vein infusion of hydrocortisone (0 to 8 hours). At the end of 8 hours the infusion site was "switched" to the portal vein. Steroid concentrations in splenic arterial and portal venous plasma were determined at hourly intervals thereafter.

they were collected and the frozen plasma was stored for subsequent analysis. The sampling volume was immediately replaced by fresh whole blood from a donor dog.

Two groups of dogs were studied. The first group consisted of 5 animals (dogs 1, 4, 5, 7, and 9) in which the effect of operation was observed. Eight hours after the beginning of the steroid infusion they were anesthetized lightly with pentobarbital. An abdominal exploration was performed through a 15 centimeter mid right rectus incision. The total operative procedure required 60 minutes in each instance and served as the operative "stress" in these experiments. Blood sampling was continued thereafter at hourly intervals for 6 hours.

The second group consisted of 2 animals (dogs 3 and 10) which were not subjected to operation. Instead, at the end of 8 hours, the hydrocortisone infusion was transferred from the leg vein catheter to the portal vein catheter. Again, after this change in the steroid infusion site, the sampling was continued at hourly intervals for a period of 6 hours.

Free 17-hydroxycorticosteroid values were determined by the Nelson-Samuels method, using a hydrocortisone standard. Our results obtained with this procedure have been consistently reproducible, ±10 per cent at concentrations between 5 and 20 milligrams per cent.

RESULTS

Operative experiments (*dogs 1, 4, 5, 7, and 9*). The results obtained in the 5 experiments in which the effect of operative "stress" was observed are presented in Table I and Figure 1.[1] The plasma free 17-hydroxycorticosteroid content of samples, drawn at hourly intervals, beginning 4 hours after the start of the infusion, was essentially stable in specimens from all vessels sampled prior to operation. No significant difference was found between the mean corticoid concentrations in portal venous and splenic arterial blood in any of the experiments reported herein.

After operation, the mean steroid concentration in all samples from portal and hepatic veins and splenic artery rose consistently. Considered individually, the increment in mean portal vein steroid concentration is statistically significant only in dog 4 ($P<0.05$)[2] and in dog 7 ($P<0.01$). Similarly, mean splenic arterial free 17-hydroxycorticosteroid concentration increased postoperatively in all experiments in which this sample was obtained. Again the magnitude of the rise is significant only in dog 7, ($P<0.01$). As noted before, the concentration of corticosteroid was the same in the portal vein and splenic artery. Therefore, we have grouped these data together for the experiments in which both were obtained. With the greater number of observations thus available for statistical analysis, the postoperative rise in steroid concentration in splenic arterial and portal venous blood assumes significance in experiments 5 ($P<0.05$) and 9 ($P<0.02$).

A postoperative rise in the steroid concentration in hepatic venous blood was observed in all experiments. The magnitude of this rise, though consistent in each experiment, is probably significant only in dogs 7 and 9 ($P<0.02$). The mean portal vein–hepatic vein steroid concentration difference decreased from 8.2 micrograms per cent to 7.2 micrograms per cent in dog 5 postoperatively. In the remainder of the dogs, a small increase in this gradient was found; this increase is in no dog statistically significant. It is at least clear, however, that

[1] Dog No. 7 expired 2 hours after operation from accidental intra-abdominal hemorrhage which occurred about the sampling catheters. The experiment was successfully completed in the remaining 4 dogs.

[2] Arithmetic means were compared using the formula:

$$T = \frac{\overline{X}_1 - \overline{X}_2}{\hat{S}} \sqrt{\frac{N_1 N_2}{N_1 + N_2}}$$

Where $\overline{X}_1$ and $\overline{X}_2$ are the respective means,
N_1 and N_2 are the respective degrees of freedom, and
$\hat{S}$ is derived from the formula.

$$\hat{S} = \sqrt{\frac{\Sigma(X - \overline{X}_1)^2 + \Sigma(X_2 - \overline{X}_2)^2}{N_1 + N_2 - 2}}$$

Probability "P" was derived from the resultant "T" value by reference to an appropriate table (Fisher and Yates, *Statistical Tables for Biological, Medical and Agricultural Research*, Edinburgh: Oliver and Boyd Ltd., 1938).

a consistent decrease in the steroid concentration gradient between portal and hepatic vein was not found postoperatively. These data therefore do not substantiate the occurrence of a decrease in the hepatocellular capacity for steroid metabolism following trauma.

Experiments 3 and 10. After a constant infusion of hydrocortisone into a limb vein for 8 hours, the injection site was changed to the portal vein. The results obtained in these animals are presented in Table II and Figure 2. Again in these experiments, mean portal vein and splenic arterial concentrations were similar during the first period of study. After alteration of the infusion site to the portal vein, samples were no longer obtained from this source.

In experiment 3, altering the infusion site resulted in an 8 microgram per cent fall in mean splenic arterial steroid concentration and a coincident 4.8 microgram per cent rise in the mean hepatic venous concentration. Similar studies in experiment 10 reveal no change in the mean splenic arterial concentration with switch in the hydrocortisone infusion site. A 4.5 microgram per cent concentration rise was observed in hepatic venous blood. During the period of infusion into the portal vein, the hepatic venous and splenic arterial 17-hydroxycorticosteroid values were the same in both dogs.

DISCUSSION

With infusion of hydrocortisone into a peripheral vein, there was no significant difference in the concentrations of free steroid between specimens from splenic artery and portal vein. When the site of infusion was changed from a peripheral vein to the portal vein, no significant difference was found in the concentration of 17-hydroxycorticosteroids in hepatic venous as compared with splenic arterial blood. Based on this lack of concentration gradient across the splanchnic or pulmonary circulations, these data provided no evidence of extrahepatic transformation or concentration of hydrocortisone. Contrasted with this observation was the consistently appreciable concentration gradient across the liver. It would therefore appear that the liver is the major site of hydrocortisone metabolism in the dog.

In the 5 adrenalectomized dogs whose plasma concentrations of 17-hydroxycorticosteroids were maintained at stable levels by the constant infusion of hydrocortisone, operation resulted in a rise in 17-hydroxycorticosteroids concentration in peripheral arterial and portal venous samples. There was a concomitant rise in the hepatic venous steroid concentration, such that the difference between portal venous and hepatic venous concentration remained relatively unchanged except in dog 7 in which the difference increased appreciably and in dog 5 in which it decreased slightly. If the postoperative change in the rate of metabolism of hormone were explained solely on the basis of impairment of hepatocellular function with no associated alteration in hepatic blood flow, a decrease in the difference between portal and hepatic venous corticosteroid concentration would have been anticipated in all experiments. Such a decrease was not found; therefore, no evidence was obtained that a decrease in the rate of hepatocellular metabolism of hydrocortisone occurs postoperatively. This conclusion coincides with the results of Hechter and associates (8) to which reference has been made.

Could a coincident decrease in hepatic blood flow after operation explain the observations? The reserve capacity of the liver, per se, for steroid metabolism appears to be so great as to make this possibility unlikely. Drastic change in hepatic blood flow would be required to alter appreciably the rate of steroid metabolism if this were the only variable involved. The majority of hydrocortisone in plasma is protein bound, and this must be taken into consideration. If only the unbound fraction of steroid were available to the liver for metabolism, then smaller alterations in blood flow could be reflected in changes in the over-all rate of hydrocortisone metabolism. Indeed, a delay in the disappearance rate of hydrocortisone

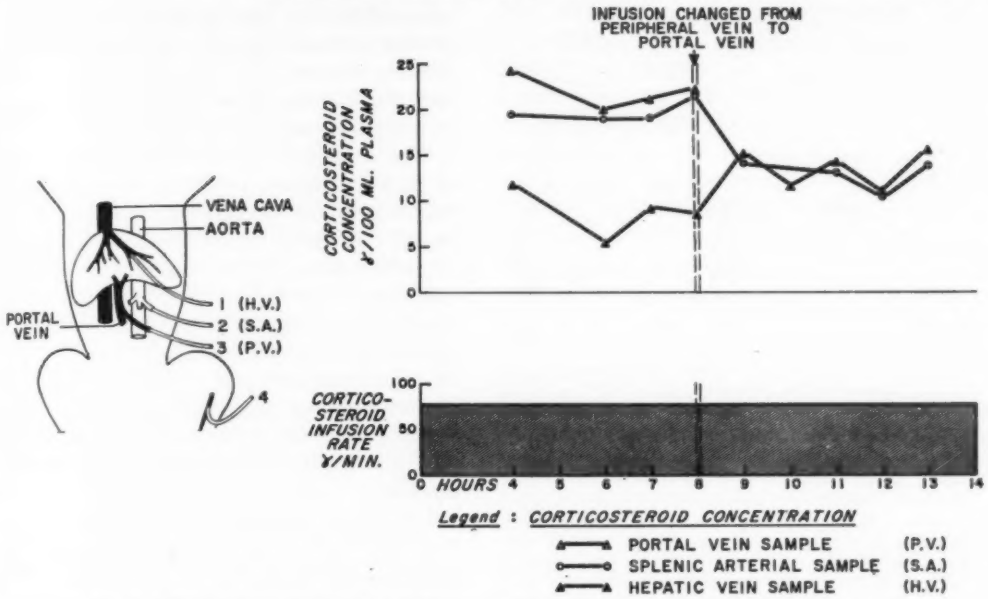


FIG. 2. Effect of increasing portal vein concentration of corticosteroid in dog 3. After an 8 hour constant infusion of hydrocortisone via a peripheral vein (*4*), the infusion site was changed to the portal vein (*PV, 3*). The infusion rate remained constant. This change in infusion site resulted in a rise in the 17-hydroxycorticosteroid concentration in hepatic venous (*HV, 1*) plasma. A coincident fall in splenic arterial (*SA, 2*) plasma concentration was noted, indicating an increase in the over-all rate of steroid metabolism resulting from the change in infusion site.

has been claimed in the dog, coincident with changes in hepatic blood flow produced by portal vein and hepatic artery ligation.

Marks and Leaf have noted the correlation between renal 17-hydroxycorticosteroid excretion and glomerular filtration rate. Thus, the known decrease in glomerular filtration rate following operation could, in part at least, be responsible for the observed findings. Renal excretion, however, accounted for the disappearance of a sufficiently small fraction of the total infusion dose of hydrocortisone in these animals that a relatively large alteration in renal function would be required to account for the observed decrease in the rate of disappearance of hormone. Such marked alterations in glomerular filtration rate do not occur.

A decrease in the rate of "peripheral transformation" of 17-hydroxycorticosteroids could result in a decrease in the over-all metabolism of the hormone. This remains a possibility, the significance of which we cannot evaluate from presently available data.

The rise in corticoid levels could result from the release of a body "store" of unaltered hydrocortisone. We find no evidence for the release of such a body store of this hormone after operation. On the contrary, Firschein and associates have indicated that there is a delay in release of hormone from muscle following "stress." They found that 5 minutes after the injection of cortisol 4-C14 in rats, 50 per cent of the radioactivity was recovered from muscle. In the normal animal, this quantity decreased rapidly so that after 1 hour only 20 per cent remained. In rats subjected to tourniquet shock, this rate of clearance of radioactivity from muscle was markedly delayed. In fact, the activity of liver and muscle in the "stressed" rats did

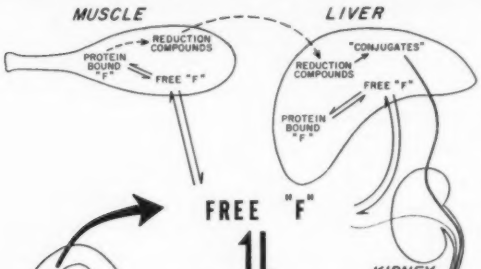


FIG. 3. Scheme of the distribution of hydrocortisone in the intact organism. Free hydrocortisone ("F"), secreted by the adrenal cortex, enters the vascular "pool" via the adrenal veins. In blood, the largest fraction is reversibly bound to protein. The unbound fraction, being free to migrate across capillary and cell membrances, enters cells (here illustrated by muscle and liver). By virtue of this migration, a small fraction of unconjugated hormone ("free F") is excreted in the urine. Within cells, the unbound hydrocortisone may be either reversibly bound with protein again, or may undergo reduction. The quantitatively most significant fraction of this metabolic destruction (reduction) occurs within the liver. Subsequent to their reduction, these compounds are conjugated with glucuronic acid. The site of actual conjugation remains unknown. The resultant conjugates of the reduced steroids, being readily soluble in water, are excreted in the urine.

not decrease between 15 and 60 minutes. Plasma activity in these animals did, however, fall gradually during this period, suggesting that delay in the release of hydrocortisone from tissue, rather than a defect in hepatic metabolism, is the primary factor in producing the decreased rate of disposal of adrenal cortical steroid following stress. This observation suggests that the distribution and release of hydrocortisone in tissue is impaired after trauma. Whether this results from an alteration in the protein-steroid bond in tissue or in plasma remains unknown. It seems likely that a change in the facility with which hydrocortisone is distributed in the body explains the rise in peripheral corticoid levels seen in the present operative experiments.

It is further interesting to note that bromsulphalein is, like hydrocortisone, protein bound. Thus, the correlation of decreased bromsulphalein and steroid clearance following operation may be manifestations of a similar alteration in protein binding, and not of a decrease in hepatocellular function, as has previously been suggested.

The increased portal vein concentration of hydrocortisone, resulting from direct infusion into the portal venous cathether in Dog 3, produced an increase in the rate of hepatic corticosteroid transformation (as evidenced by a fall in the mean splenic arterial 17-hydroxycorticosteroid levels from 19.6 to 12.8 micrograms per cent). In dog 10, which received a hydrocortisone infusion of one-half that administered to dog 3, altering the steroid infusion site did not result in a perceptible change in arterial concentration.

Levin and associates have noted an increase in tissue binding and in degradation of hydrocortisone in liver slices with increasing concentrations of steroid. Binding increased in direct one-to-one proportion with increasing concentrations of hydrocortisone. Degradation also increased, but in less than a direct proportion to the increasing concentration of hormone. That an increase in the rate of metabolism of hydrocortisone in man is directly proportional to the increased availability of hormone is emphasized by the work of Peterson and associates. They found no alteration in the disappearance rate of cortisol 4-C14 from plasma with varying quantities of simultaneously injected carrier hydrocortisone. The over-all rate of metabolism in the intact human, therefore, is directly proportional to availability. It is suggested, then, that the rate of hepatocellular transformation of 17-hydroxycorticosteroids is not the rate-limiting step in determining the blood levels of measurable hormone in the intact organism. Rather, some other function, probably protein binding of hydrocortisone, governs its rate of metabolism.

Protein binding of steroid in plasma could restrict its migration across capillary and cell membrane, such migration being limited to the unbound fraction of hydrocortisone

(Fig. 3). Since steroid transformation appears to occur largely within the hepatic cell, it is apparent that the state of protein binding of hydrocortisone in plasma (as well as in peripheral tissues) may regulate the rate of corticosteroid metabolism by the liver.

The anomalous results in experiment 10 remain unexplained. The infusion rate of hydrocortisone in this animal was only one-half that administered in the previous experiments, and correspondingly small plasma concentrations of 17-hydroxycorticosteroids were observed. Changing the infusion site to the portal vein catheter was accompanied by no perceptible alteration in the rate of hydrocortisone metabolism (as evidenced by the lack of change in the peripheral arterial concentrations). At these low concentrations, however, the limits of error of the analytic method approximate the anticipated change in steroid concentration, which may well have been missed.

The present results support the thesis that the liver plays a passive role in determining the over-all disappearance rate of hydrocortisone in the intact organism. The hepatic capacity for steroid metabolism per se exceeds that required for quantities of cortical steroid present in biologic situations. The liver is limited in the rate at which it may transform these substances by their availability to it. Availability, in turn, is dependent at least partially upon hepatic blood flow and the status of protein-steroid binding in plasma and in the peripheral tissues.

Cortisol in plasma has been found to be largely protein bound. This binding involves at least two systems of the plasma proteins. The first is albumin, which has a relatively great capacity and low affinity for hydrocortisone binding. The second is associated with the alpha globulin area in the electrophoretic separation which has a limited capacity for binding, but relatively great affinity. This latter system has been named "transcortin."

That increases in the hydrocortisone binding capacity of plasma may occur in association with a variety of physiologic and pathologic states has been suggested by Daughaday. Indeed, an increase has been documented by Slaunwhite and Sandberg in association with pregnancy. It is not known whether this change in protein binding capacity results from an alteration in the nature of the bond itself or from changes in the concentration of the binding protein fraction. The latter possibility is suggested by the work of Chanutin and Gjessing. They were able to document increases in the plasma alpha globulin fraction in dogs following injury. Unfortunately, no studies of the cortisol-binding capacity of plasma in postoperative animals or patients have been reported.

SUMMARY

1. Evidence for the occurrence of a delay in the rate of disposal of hydrocortisone from the circulation after trauma has been reviewed. The cause of this delay remains unknown. Many workers have ascribed it to an impairment in hepatic function following trauma.

2. Considerable evidence has been reviewed which casts doubt on the role of change in hepatic function alone in the initiation of this metabolic change.

3. Adrenalectomized dogs with chronic inlying arterial, portal venous, and hepatic venous sampling cannulas have been studied during constant peripheral venous hydrocortisone infusion before and after an operation. After 4 hours, constant infusion resulted in stable plasma concentrations of free 17-hydroxycorticosteroids. With operation these concentrations in arterial, portal, and hepatic venous blood increased consistently. The hepatic concentration gradient (the free steroid concentration difference between hepatic artery and portal vein and the hepatic vein) remained the same or increased slightly after operation. This result is incompatible with the occurrence of a decrease in the hepatocellular capacity for steroid metabolism following operation.

4. An additional 2 adrenalectomized dogs

were studied. After 8 hours, the constant hydrocortisone infusion site was changed from a peripheral vein to the previously catheterized portal vein. This change resulted in an increase in the rate of steroid metabolism in one dog. In the other, no change was apparent. This inconsistency is explained on the basis of lesser concentrations of 17-hydroxycorticosteroids in the latter instance. At this level the accuracy of the method was insufficient to allow for identification of a change in the metabolic rate.

5. These data are thought to be consistent with the following hypothesis:

The liver cell itself has a much greater capacity for steroid metabolism than is ordinarily required by steroid concentrations which are experienced in biologic situations. The rate of steroid metabolism is limited by the availability of hormone to the sites of metabolism. Availability, in turn, is dependent upon the status of protein binding in tissue as well as in plasma. This determines the distribution of hydrocortisone across vascular and cellular membranes. It is proposed that change in this protein–steroid bond initiates the change in steroid metabolism experienced after trauma.

REFERENCES

1. Beecher, H. K., Simeone, F. A., Burnett, C. H., Shapiro, S. L., Sullivan, E. R., and Mallory, T. B. I. The internal state of the severely wounded man on entry to the most forward hospital. Surgery, 1947, 22: 672.
2. Brown, H., Willardson, D. G., Samuels, L. T., and Tyler, F. H. 17-hydroxycorticosteroid metabolism in liver disease. J. Clin. Invest., 1954, 33: 1524.
3. Chanutin, A., and Gjessing, E. C. Electrophoretic analysis of urea after treating dogs with chloroethyl vesicants. J. Biol. Chem., 1946, 165: 413.
4. Cole, J. W., and Leuchtenberger, C. Cellular changes during surgical stress—I, morphologic alterations in hepatic cells. Surg. Gyn. Obst., 1956, 102: 702.
5. Daughaday, W. H. Binding of corticosteroids by plasma proteins. Arch. Int. M., 1958, 101: 286.
6. Firschein, H. E., DiVenuto, F., Fitch, W. M., Pearce, E. M., and Westphal, U. Distribution of injected cortisol - 4-C14 in normal and shocked rats. Endocrinology, 1957, 60: 347.
7. Ganong, W. F., Bernhard, W. F., and McMurray, J. D. The effect of hypothermia on the output of 17-hydroxycorticoids from the adrenal vein in the dog. Surgery 1955, 38: 506.
8. Hechter, O., Frank, E., Caspi, E., and Frank, H. Corticosteroid metabolism in liver in vivo metabolism of cortisone and cortisol by dog liver. Endocrinology, 1957, 60: 705.
9. Hechter, O., Solomon, M.M., and Caspi, E. Corticosteroid metabolism in liver: studies on perfused rat liver. Endocrinology, 1953, 53: 202.
10. Ingle, D. J., Ward, E. O., and Kuizenga, M. H. The relationship of the adrenal glands to changes in urinary non-protein nitrogen following multiple fractures in the force-fed rat. Am. J. Physiol., 1947, 149: 510.
11. Lefemine, A. A., Marks, T. J., Teter, J. G., Leftin, J. H., Leonard, M. P., and Baker, D. V. The adrenocortical response in surgical patients. Ann. Surg., 1957, 146: 26.
12. Levin, M. E., Danghaday, W. H., and Bremer, R. Tissue binding of hydrocortisone. J. Laborat. Clin. M., 1955, 45: 833.
13. Marks, L. J., and Leaf, A. The relationship of the renal excretion of adrenal corticoids to variations in renal hemodynamics. J. Clin. Invest., 1953, 32: 813.
14. Miller, L. L., and Axelrod, L. R. Cortisone metabolism in perfused normal and experimental cirrhotic rat liver. Metabolism, 1954, 3: 438.
15. Murray, J. O. S., Marks, L. J., Colombo, F. V., Burrell, J., Leftin, J. H., and Leonard, M. P. The effect of surgical operations on the plasma clearance of infused cortical. Ann. Surg., 1958, 148: 951.
16. Nelson, D. H., and Samuels, L. T. Report of a method for the determination of 17-hydroxycorticosteroids in blood: 17-hydroxycorticosterone in the peripheral circulation. J. Clin. Endocr. Metab., 1952, 12: 519.
17. Peterson, R. E., Wyngaarden, J. B., Guerra, S. L., Brodie, B. B., and Bunim, J. J. The physiologic disposition and metabolic fate of hydrocortisone in man. J. Clin. Invest., 1955, 34: 1779.
18. Sandberg, A. A., Eik-Nes, K., Samuels, L. T., and Tyler, F. H. The effects of surgery on the blood levels and metabolism of 17-hydroxycorticosteroids in man. J. Clin. Invest., 1954, 33: 1509.
19. Schmidt, C. R., Vanruk, R. T., and Chesky, V. E. Clinical studies of liver function—I, the effect of anesthesia and certain surgical procedures. Am. J. Surg., 1942, 57: 43.
20. Scott, R., Howard, J. M., and Olney, J. M. Hepatic function of the battle casualty; the systemic response to injury. Surg. Gyn. Obst., Internat. Abst. Surg., 1956, 102: 209.
21. Shoemaker, W. C., Walker, W. F., VanItallie, T. B., and Moore, F. D. A method for the simultaneous catheterization of major hepatic vessels in a chronic canine preparation. Am. J. Physiol., 1959, 196: 315.
22. Slaunwhite, W. R., and Sandberg, A. A. Transcortin: a corticosteroid binding protein of plasma. J. Clin. Invest., 1959, 38: 384.
23. Steenburg, R. W., Lennihan, R., and Moore, F. D. Studies in surgical endocrinology—II, the free blood 17-hydroxycorticosteroids in surgical patients, their relation to urine steroids, metabolism, and convalescence. Ann. Surg., 1956, 143: 180.

SURGICAL ANATOMY OF THE INGUINAL REGION BASED UPON A STUDY OF 500 BODY-HALVES

BARRY J. ANSON, Ph.D.(Med.Sc.), Chicago, Illinois,
EDWARD H. MORGAN, M.D., Seattle, Washington, and
CHESTER B. McVAY, M.D., F.A.C.S., Yankton, South Dakota

NEARLY 150 YEARS AGO the works of Peter Camper, Sir Astley Cooper, Scarpa, Hesselbach, and Jules Cloquet, dealing with the anatomy of the region of inguinal hernia, were published with many beautifully executed engravings. In 1841 an extremely sound piece of work by Sir Thomas Morton appeared; then, in 1898 the anatomist, Paul Eisler, and in 1912 the famed surgeon, Eugene Polya, presented reports of their comprehensive studies of the inguinal region. Unfortunately, the accuracy of information concerning inguinohypogastric anatomy extant today does not compare with that established by the aforementioned investigators. Furthermore, the rate of recurrence of inguinal hernias treated surgically by methods based upon incorrect anatomy persists with disturbing frequency. For these reasons, the region of inguinal hernia was restudied in a large number of specimens in order to clarify descriptions of certain structures about which confusion currently exists and to determine the incidence of departures from the anatomic "normal" presented in conventional accounts. Each of the strata was studied individually as to its extent and the character of its constituents.

MATERIAL AND METHODS

For this study the inguinohypogastric regions of 500 body-halves obtained from 254 consecutive specimens of adult cadavers (21 female subjects and 233 males) were examined. Specimens possessing a persistent patent processus vaginalis into which there was no herniation of abdominal viscera were included (17 body-halves, occurring in 13 specimens, 4 bilaterally, 5 on the right side, 4 on the left).

For each subject, permanent records of the extent and character of the inguinal layers were made by outlining on glass the essential gross features. These were then transferred to tracing paper, together with details of structure added freehand.

The following features are hereinafter described and illustrated: the aponeurosis of the external oblique, to include inguinal fault in its fibers (Figs. 1 to 5); the internal oblique layer, as examined from both the external and internal aspects (Figs. 6 to 10); the transverse abdominal muscle and its internal investing (transversalis) fascia (Figs. 11 to 15); the inguinal part of the tendon of the rectus muscle; the subserous (properitoneal or preperitoneal) layer of fatty connective tissue.

EXTERNAL OBLIQUE LAYER

The external oblique layer of the abdominal wall is a trilaminar structure composed of a musculoaponeurotic portion invested on each surface by a fascial layer (Fig. 1). The stratum is continued about the spermatic cord and testis as the external spermatic (or intercrural) fascia.

The tendinous continuations of the external oblique muscle fibers, the aponeurotic fibers, descend inferomedialward to inguinal attachments.

Near the pubic tubercle some of the fibers of the inguinal ligament diverge posteriorly in a transverse plane to a relatively

Contribution No. 646 from the Department of Anatomy, Northwestern University Medical School, Chicago.

FIG. 1. External oblique muscle. Photomicrograph of a section from an area superolateral to the aponeurotic cleft. Showing the groups of aponeurotic fibers and the investing fascial layers of deep (muscle) fascia. ×45.

narrow attachment on the pubic pecten, thus forming the lacunar ligament of Gimbernat; other fibers of the inguinal ligament course in fan-shaped manner upward and medialward in a coronal plane behind the external oblique aponeurosis, to fall in the plane of the subjacent internal oblique aponeurosis. Polya has called this group of fibers the reflected inguinal ligament.

At a point a variable distance superolateral to the pubic tubercle, fibers of the aponeurosis begin to diverge to form a triangular opening, bounded by superomedial aponeurotic fibers (the superior crus), and by inferolateral aponeurotic fibers (the inferior crus). Through the basal portion of this aponeurotic cleft pass the spermatic cord in the male and the round ligament in the female, carrying the fascial layers outward in annular fashion, to form the so-called subcutaneous inguinal ring. Often the circular character of the origin of this investment of the cord is accentuated by the presence of intercrural fibers. These are aponeurotic elements of the external oblique within the investing fascial layers of the aponeurosis, which course across the area of the intercrural cleft instead of following the others in parallel course.

Muscular portion of the external oblique layer in the inguinal region. With rare exception, the external oblique layer in the inguinal region of the abdominal wall is entirely aponeuroticofascial in structure. In a series of 130 inguinohypogastric regions, muscle fibers of the musculus obliquus externus abdominis extended below the interspinous line bilaterally in a single instance, in 2 cases on the right side alone, and in 4 on the left. In none did the muscle fibers extend into the inguinal region for a distance exceeding 1.5 centimeters.

Aponeurotic portion of the external oblique layer. In the course of the examination of the aponeurotic portion of the external oblique layer in the inguinal region, variation in the size of the individual tendon fibers and in their distribution was noted. Some of the aponeurotic sheets were composed of fibers, fine and hairlike in quality; others were made of bandlike strands. Usually the fibers were closely approximated, but in some cases fusiform interspaces were produced by divergence of the aponeurotic fibers, much as the aponeurotic cleft is formed. Morton noted the presence of these defects. The long axis of the fault lay in the direction taken by the aponeurotic fibers, bridged by the investing fasciae of the flat tendinous sheet. In a series of 200 inguinal regions, this type of defect appeared 31 times (15 per cent of cases). In 7 instances the defect was located beneath the inferior crus or inferolateral to the aponeurotic cleft; in the remaining cases the defects were found above and medial to the cleft (where they overlay the rectus muscle). Through 12 of these coursed either the ilioinguinal or the iliohypogastric nerve. The hiatuses varied in size from 0.5 centimeter in length and 0.3 centimeter in width, to 8 centimeters in length and 1 centimeter in width (Fig. 2).

Aponeurotic cleft. The regularly present fusiform cleft in the aponeurosis of the external

oblique, through which pass the spermatic cord in the male and the round ligament in the female, is formed by the divergence of aponeurotic fibers in the inferomedial part of the inguinohypogastric region.

Far from being a hiatus of "standard" and, therefore, predictable length, the intercolumnar fault in the aponeurosis of the external oblique is highly variable in extent—occasionally extending upward and lateralward beyond the anterior superior spine of the ilium (Fig. 2). In a few instances the hiatus is small, having little more than the dimensions of an annular opening—the "ring" of the familiar anatomic and surgical descriptions. Although the cleft was confined to the lower half of the area between the midline and the iliac spine in more than 80 per cent of the cases, in the remaining considerable fraction of the total number of measured specimens it extended superolaterally to and beyond the limit of inguinal territory.

Since the lower part of the gap lies over the body of the pubic bone, a triangular gap remains in the parietal wall—its base being the superior edge of the os pubis. The relationship of the aponeurotic cleft to the area of inguinal hernia was determined by noting the extent of the triangular gap overlying Hesselbach's triangle in 66 body-halves (from 33 specimens: 5 females, 28 males). The apex of the cleft in 7 specimens (11 per cent) lay at a point less than one-half the distance from the pubic tubercle to the inferior epigastric artery in a line following the long axis of the cleft (Fig. 4, at *a*); in 34 (52 per cent) the apex was situated between the epigastric vessels and the midpoint of a line between the pubic tubercle and the inferior epigastric vessels (Fig. 4, at *b*); in 24 specimens (37 per cent) the upper angle of the cleft lay beyond the inferior epigastric vessels, as shown in Figure 4, at *c*.

In the examination of the inguinohypogastric region of 200 body-halves, the aponeurotic cleft was highly variable in 3 instances (Fig. 3).

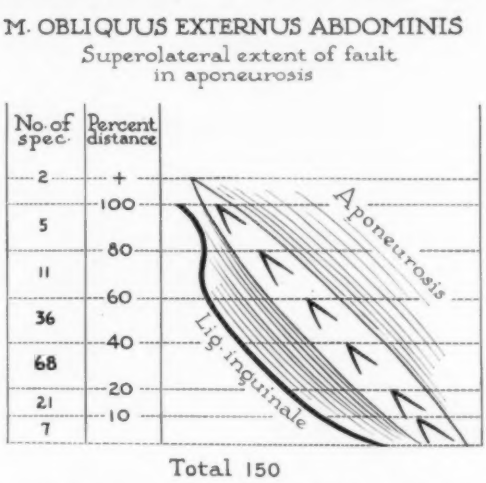


FIG. 2. External oblique aponeurosis. Variation in the length of the triangular aponeurotic fault, shown in the relation of its apex to the anterior superior spine of the ilium. In approximately one-sixth of 150 body-halves the fault extended superolaterally beyond the midpoint in distance from the symphysis of the pubis to the anterior superior spine of the ilium.

Investing fascial layers and intercrural fibers. The aponeurosis of the external oblique is invested by external and internal layers of fascia, the outer of which (fascia innominata of Gallaudet) is the heavier. Within this layer, there occur more or less dense bands of fibrous tissue that course at right angles to the direction of the aponeurotic fibers. These fibers lie within the fascia innominata and show remarkable variations (Fig. 5).

Every textbook of encyclopedic inclusion and some other books of less ambitious textual and pictorial coverage discuss intercrural fibers with such gravity and in such detail that the unschooled dissector is led to expect their obvious and constant appearance in the area where the aponeurotic columns diverge to create the fault termed subcutaneous inguinal ring. Seemingly, their status is heightened by the persistent application of the name "intercrural fascia" to the funicular prolongation of the fascia from the external oblique aponeurosis. Actually, fibers of this nature occur in various parts of the inguinal area, in 27 per cent of in-

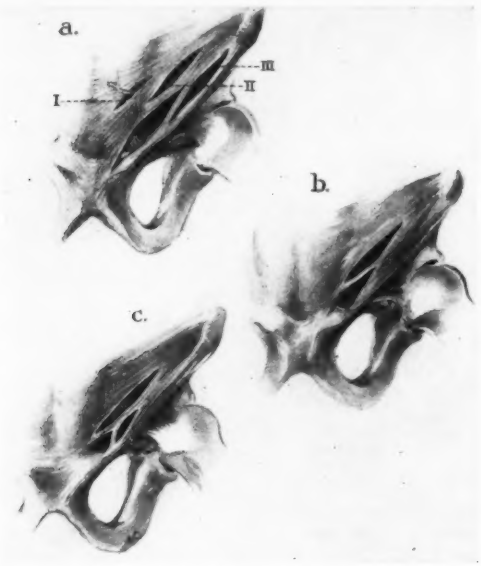


FIG. 3. Aponeurosis of the external oblique. Selected examples of accessory cleft which are related to the triangular fault for transmission of the spermatic cord. In "a" the iliohypogastric nerve passes through hiatus *I*.

stances near, but not in, the territory of the intercrural hiatus (Figs. 5a and 5l). Fibers of true intercolumnar (intercrural) placement may be distributed in any one of the following ways: limited to an apical area (Fig. 5b); occupy the latter zone and spread beyond it (Fig. 5e); occur at mid-distance (Figs. 5c and 5i) or there and beyond the apex (Fig. 5g); be present at the medial extremity or base (Fig. 5d) at both ends of the fault (Fig. 5h) or throughout the length of the intercolumnar area and beyond it (Fig. 5j), or spreading beyond the fault and across an accessory cleft (Fig. 5k); cover only the accessory cleft (Fig. 5l); occupy the entire lateral half of the fault (Fig. 5f).

Reflected inguinal ligament. According to all standard accounts, a structure termed the reflected (reflex) inguinal ligament is formed by aponeurotic fibers of the superior crus from the opposite side, which descend to an attachment on the body and tubercle of the pubis. Actually, such a triangular structure may be formed in any one of several ways. One type, described by Cruveilhier is formed by crossing of fibers of the superior crus on one side to an attachment as far lateralward as the pubic tubercle of the opposite side, lying dorsal to the superior crus of the contralateral side. In a study of 250 body-halves Anson and McVay in 1938 found this type of reflected ligament bilaterally in 1 specimen, and unilaterally in 3. In well developed form, this structure would be expected to act as a support to the inferomedial area of the cleft in the aponeurosis of the external oblique.

In a type described by Polya, fibers radiate upward in the coronal plane, immediately dorsal to the external oblique aponeurosis. These fibers of the inguinal ligament (inferior crus), arising in the region of the pubic tubercle, join the rectus sheath for an insertion into the linea alba.

In a series of 65 body-halves the present authors found such a radiation of the fibers of the inguinal ligament in every specimen. The reflected ligament (of Polya) was found to act as a supportive structure in the inferomedial area of the aponeurotic cleft in 12 of 65 body-halves (bilaterally in 3 specimens, unilaterally in 6).

A third type of triangular fibrous structure was observed once in the examination of the 200 body-halves. In this variety the ligament was formed by particularly well developed intercrural fibers that spread medialward and upward toward the linea alba from the lower area of the aponeurotic cleft. However, these fibers lay on the external surface of the external oblique aponeurosis within the fascia innominata, possibly offering support to the inferomedial part of the aponeurotic cleft.

INTERNAL OBLIQUE LAYER

In contrast to the regularly aponeurotic nature of the external oblique layer in the inguinohypogastric region, the parietal portion of the internal oblique stratum is composed almost entirely of muscle fibers.

Muscular portion of internal oblique. For the purpose of determining the degree of descent

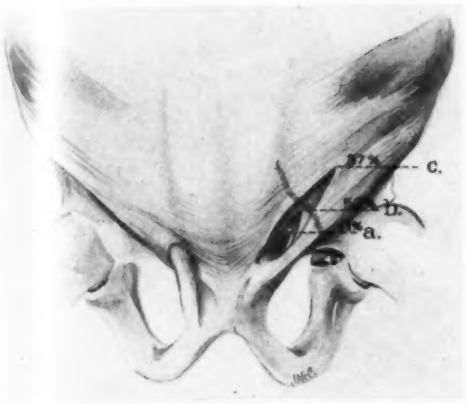


Fig. 4.

FIG. 4. Aponeurosis of the external oblique. The triangular fault shown in relation to the epigastric vessels—at the lateral boundary of the triangle of Hesselbach. In 52 per cent of 66 body-halves the apex reached the approximate position of the epigastric fold; in 37 per cent it extended beyond this fold; in 11 per cent the cleft was limited to a zone in the medial half of Hesselbach's triangle.

FIG. 5. External oblique aponeurosis. Variation in distribution of grossly evident intercrural fibers in the outer investing (innominate) fascia.

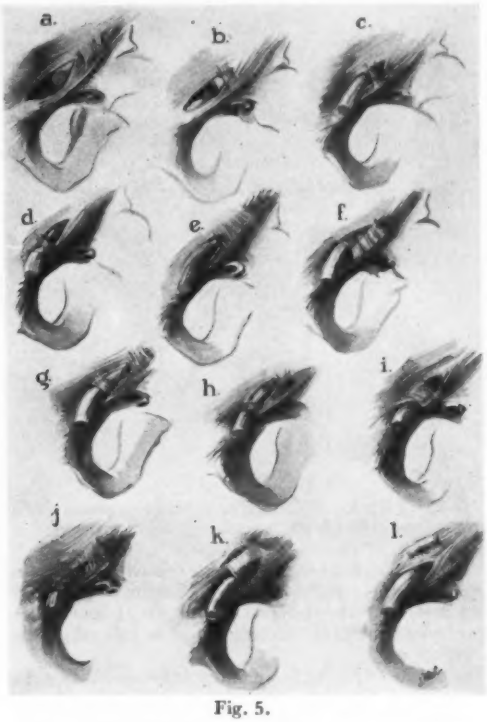


Fig. 5.

of the muscular part of the internal oblique into the inguinohypogastric region, records were taken on 500 body-halves. In each instance the inguinohypogastric region of the specimen was divided longitudinally and transversely by 10 equally spaced lines so that the extent of the muscle could be expressed roughly in terms of per cent. The medial extent of the muscle was noted at two points: (1) at its inferomedial angle, and (2) at the point where the muscle crossed a line drawn between the anterior superior iliac spines. The inferior extent of the internal oblique muscle was observed at the inferomedial angle of the muscle (Fig. 6).

The muscular part of the internal oblique layer extended inferiorly to the level of the inguinal canal in only 2 per cent of 500 body-halves. In 75 per cent of cases the fleshy part covered somewhat more than 75 per cent of the inguinal area (that is, the region caudal to a line passing transversely between the anterior superior iliac spines). However, in approximately 1 of 4 cases (23 per cent) muscular tissue occurred in only the cranial (upper) half of the inguinal wall.

In the same lot of specimens the medial extent was likewise variable (Fig. 6). In 3 of 4 specimens (75 per cent), the fleshy plaque of the internal oblique covered 75 per cent of inguinal region (measured along the inferior border of the muscle). In 7 per cent of cases the extent was greater to cover approximately 85 per cent of the area; in 18 per cent it was less.

In every case the medial border of the muscle inclined away from the midline with ascent, so that the muscular fraction of the layer was less in a plane with the interspinous line than in a plane marking its inferior margin.

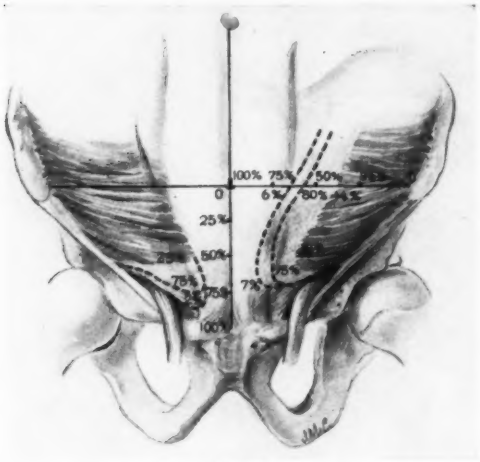


FIG. 6.

FIG. 6. Internal oblique muscle. Inferior extent (left) and medial extent (right). Statistical results, recorded in percentages of a study of 425 inguinal regions.

FIG. 7. Internal oblique layer. Anterior (ventral) aspect. Types of distribution of musculature encountered in a study of 500 body-halves. Class I, variations in those specimens (in 258) in which there was no parietal defect.

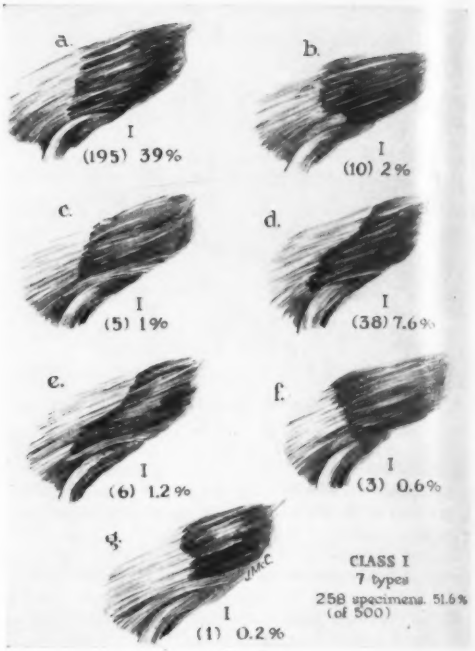


FIG. 7.

In 220 specimens, Chandler and Schadewald studied the muscular extent of the internal oblique muscle in Hesselbach's triangle. They found that it covered the triangular area completely in 21 per cent. In 46 per cent the muscle overlay at least one-half but not all of the triangle, and in 32.8 per cent the internal oblique failed to cover Hesselbach's area entirely, or it covered less than one-half of the triangle.

Contour and structure of the musculoaponeurotic portion of the internal oblique. In addition to variation in the quantity of muscle in the inguinohypogastric region, significant differences occur in contour and structure of the musculoaponeurotic portion of the internal oblique layer. In this study of 500 body-halves, three fundamental types of muscle were found. In certain of these, musculoaponeurotic deficiencies were found, in the form of slitlike gaps between divergent bundles of fibers. However, investing fascial layers of the stratum invariably bridged the defects. Masses of adipose tissue frequently filled the gaps; in some instances, herniations of adipose preperitoneal tissue passed through the transversus layer, to occupy the defects in the internal oblique stratum. Polya described and tabulated triangular deficiencies encountered in the internal oblique. In our experience, defects were fusiform rather than triangular.

In Polya's illustrations a very definite linear expanse of rectus sheath lacks musculoaponeurotic fibers of the internal oblique layer. This type of arrangement was not encountered in the current study, nor was the rectus sheath observed to be so regularly formed as shown in Polya's figures.

In this study, on the basis of presence or absence of musculoaponeurotic defects, and according to their location, three types were seen (Figs. 7 to 9). In class I the muscles exhibited none of these defects (Fig. 7). In class II, one or more musculoaponeurotic

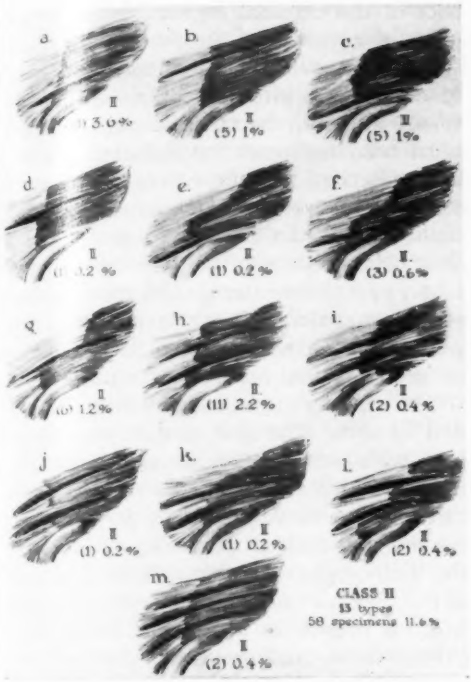


FIG. 8.

FIG. 8. Internal oblique, continued. Anterior (ventral) aspect. Types with musculoaponeurotic defects: class II, examples (in 58) of single or multiple fusiform defects above the lower margin of the muscle found in an examination of the same series of inguinal halves shown in Figure 7.

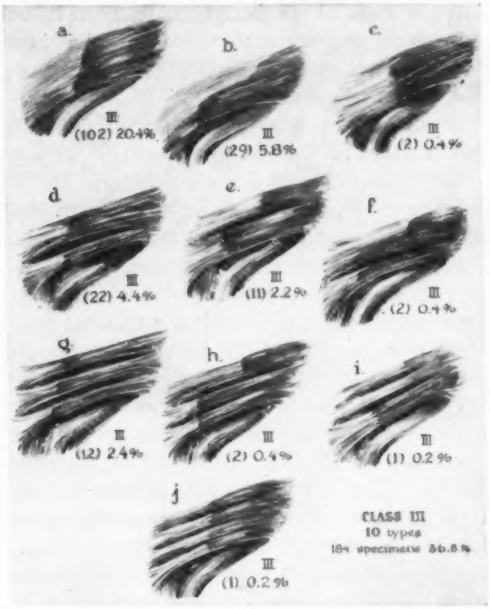


FIG. 9.

FIG. 9. Internal oblique, concluded. Anterior (ventral) aspect. Types with musculoaponeurotic defects: class III, examples (in 184) of the occurrence of one or more defects immediately above and cranial to the inguinal canal, as seen in the same series of 500 inguinal halves.

gaps occurred above the lower margin of the muscle (Fig. 8). In class III, a definite deficiency of fibers was found between the lower edge of the muscle and the spermatic cord (Fig. 9). It was found that certain of these apparent defects between cord and muscle contained thin aponeurotic fibers, obviously a poor support for a parietal region subject to intra-abdominal pressures which so often result in herniation.

Of the 500 layers examined, 258 (51.6 per cent) fell into class I. Among these were 7 minor variants that exhibited no musculoaponeurotic defects (Fig. 7). In all of the 258, the lower margin of the internal oblique aponeurosis crossed the superior edge of the pubic body at the lateral edge of the rectus tendon, or more lateral to that point. Thus, no "inguinal triangle," as described by Zimmerman, was formed.

In the greater number of examples of class I the musculature or aponeurosis was prolonged medialward along the "roof"—cranial boundary—of the inguinal canal for one-half or even greater fraction of the length (Fig. 7a,). In a few instances the muscular part followed the spermatic cord throughout the length of the canal, receding sharply in the area cranial thereto (Fig. 7d and e).

Structurally, complete layers of this class constitute a strong barricade against herniation. Furthermore, the low insertion of the aponeurotic fibers would allow the physiologic shutter action of the muscle to take place—contraction of lower internal ob-

lique muscle fibers would cause them to be approximated to the inguinal ligament and to the posterior expansion of this structure, the lacunar ligament.

In class II there were 58 specimens (11.6 per cent). The defects were variable in size —between 0.2 and 1.5 centimeters. In 39 specimens there was a single fusiform defect; in 16 cases, 2 defects; in 2, 3 defects.

Accompanying such deficiency, the internal oblique may be a layer in which musculature is rather uniformly distributed near the lower border of the layer (Fig. 8b, d, and f), or one in which banding is the striking feature (Fig. 8h to m); and the muscle may terminate medially along an almost vertical line (Fig. 8a to d) or be sharply oblique (Fig. 8e to g). The defects in this type of internal oblique are the weak areas located above the region of the inguinal canal. Therefore, the mechanics of the internal oblique insertion are such that a physiologic shutter action could occur.

In class III were placed 184 specimens, comprising 36.8 per cent of the 500 body-halves. In 51 of the specimens, one or more defects similar to those in class II muscles were found above the region of the inguinal canal.

Again, the layer in which the deficiency occurs may assume any one of several forms (Fig. 9; compare Fig. 8). The stratum may be smoothly contoured (Fig. 9a and c), steplike (Fig. 9e, f, h, and i), even in structure (Fig. 9a to c) or banded (Fig. 9d to j).

Characteristically, in this group, the deficiency in the strong musculoaponeurotic fibers lay immediately above the spermatic cord. This so-called "inguinal triangle" constitutes a structural defect of the inguinal canal in the lower part of Hesselbach's area. The high insertion of the internal oblique aponeurosis in these specimens would prevent an adequate shutter action when the muscle contracts. In this type of muscle there is an anatomicophysiologic deficiency in the region of the inguinal canal, particularly in the area of direct hernia.

Accessory internal oblique. In the lateral aspect of the inguinal region, caudal to the point of entrance of the ascending branch of the deep circumflex iliac artery into the space between internal oblique and transversus muscles, the stratification of layers often becomes somewhat indistinct. In this area, fibers of the internal oblique muscle and the transversus muscle often are indistinguishable from each other at the site of their origins; some of the fibers of common origin pass to the internal oblique layer and others to the transversus layer, forming a well defined band described by Chouke as an accessory internal oblique muscle.

The accessory muscle arises from the medial lip of the iliac crest, and its aponeurosis fuses with that of the transversus muscle in the formation of the rectus sheath. Typically, it is a narrow band, separated from the internal oblique proper by a branch of the iliohypogastric nerve and by a branch of the deep circumflex iliac artery. Chouke found it present in 219 of 272 body-halves (81 per cent), Anson and McVay in 40 per cent of 250 body-halves. In our specimens, the width of the accessory muscle varied from 1 to 5 centimeters (compare figure on page 236, Anson, 1950). In a few instances the muscle was composed of more than one band of fascicles separated by distinct fascial gaps.

In those instances in which the accessory muscle extends caudal to the lower margin of the transversus muscle (which usually lies high in the inguinal region), it may function as an additional musculoaponeurotic support to the internal oblique. Should the lower margins of both internal oblique and transversus muscles be located high in the inguinal region, the accessory internal oblique—which extends caudal to the lower margins of the two muscles—would then serve as the only available musculoaponeurotic support cranial to the level of the inguinal canal.

In this connection the following statistical results are of interest. In an examination of 218 body-halves, from 110 specimens, an accessory muscle was found in 73 of the

halves (33.5 per cent). In 44 of the 73 (60 per cent) the muscle lay above the caudal margins of the internal oblique and transversus muscles (Fig. 10a). In 27 instances (37 per cent) the accessory band extended caudal to the lower margin of the transversus musculoaponeurotic layer, and furnished musculoaponeurotic support to the area between the separated caudal margins of the internal oblique and transversus layers (Fig. 10b). In 2 cases (3 per cent) the accessory internal oblique muscle lay caudal to the inferior margins of both muscles, and there served as the only musculoaponeurotic support to the superolateral region of the inguinal canal (Fig. 10c). In 7 instances the accessory muscles were composed of 2 bands of fasciculi separated by distances up to 2 centimeters, and 1 specimen exhibited an accessory muscle consisting of 3 separated bands.

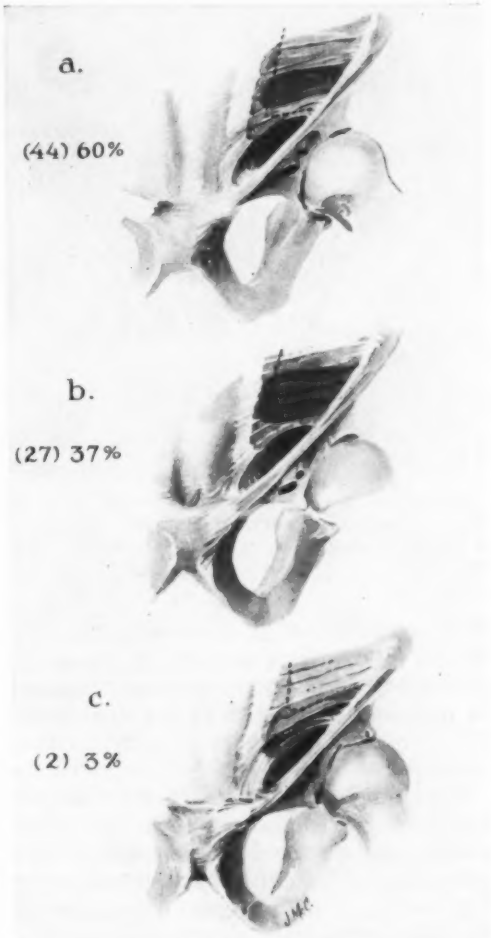


FIG. 10. Accessory internal oblique muscle (dark ones). Types determined on the basis of relation to the inferior (caudal) margin of the subjacent transverse abdominal muscle (dotted line) and the internal oblique muscle (lightly shaded). From an examination of 218 body-halves.

TRANSVERSUS LAYER

Generally speaking, the muscular part of the transverse abdominal layer in the inguinal region is a lesser component than are its aponeurosis and fascia; and in some specimens the transversus layer in the lower inguinal region is composed entirely of the apposed external and internal investing fasciae of the stratum—muscle fascicles being totally absent.

In 405 specimens the inguinal portion of the transversus layer was examined for the position of, and for the extent of, its muscular portion. As was done in the case of the internal oblique muscle, the medial extent of the muscle was observed at two points: (1) where the medial border crossed a line connecting the anterior superior iliac spines, and (2) the position of the inferomedial angle. The inferior extent of the transversus abdominis muscle was also observed at its inferomedial angle (Fig.11).

It has been established that in a surprisingly large number of cases, the muscular part of the internal oblique failed to extend caudalward as far as the inguinal canal and medialward as far as the lateral border of the rectus muscle (Fig. 6). Measurements made on the fleshy part of the transverse abdominal reveal even greater deficiency—and consequent loss of effectiveness as a barricade against herniation.

In approximately 2 of 3 instances (67 per cent of 425 body-halves), the muscle covered only the cranial (upper) half of the inguinal region (Fig. 11). In about 20 per cent of

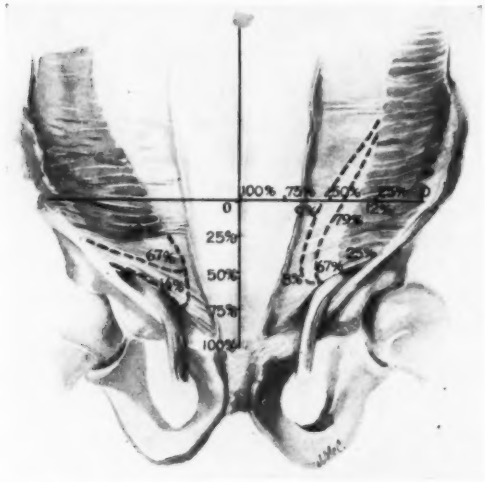


FIG. 11. Transverse abdominal muscle. Inferior extent (left) and medial extent (right). Statistical results, shown in percentage-occurrence, of a study of 425 inguinal regions.

cases the muscular part covered only the cranial fourth. The smallest lot included those cases (14 per cent) in which the muscle reached the "roof" of the inguinal canal in some part of its extent—actually, the lateral segment only.

Regarding medial extent, it may be said that no case was encountered in which the muscle reached the lateral margin of the rectus (Fig. 11). Actually, in approximately 2 of 3 instances (67 per cent) the muscle, at the inferior border, covered only one-half of the area along a transverse line between the midline of the body and the anterior superior iliac spine. In 25 per cent of cases the distance was greater; in only 8 per cent was it less. Here, matching contour of the internal oblique, the medial border of the transverse abdominal muscle fell away from the midline in ascent from the area of the inguinal canal to that of the interspinous line.

Chandler and Schadewald tabulated the extent of the transversus in the triangle of Hesselbach in 220 specimens, finding that the muscle entirely covered the triangular area in 4.2 per cent of cases, one-half or more of it in 40.5 per cent, and less than one-half or none in 55.3 per cent of the specimens.

Matching variation in the internal oblique layer, considerable differences were discovered in the structure of the musculoaponeurotic portion of the transversus stratum. Since the aponeurosis of the transversus is more complicated in contour and in attachments than that of the internal oblique, it was considered advisable to study the muscular and aponeurotic segments of the layer separately.

In 100 inguinohypogastric regions, the following 7 definite types of transversus were found. Muscles of type I possessed regular medial and inferior borders joined to form a sharp, clearly defined inferomedial angle (Fig. 12a); incidence, 75 specimens. Those of type Ia resembled type I, but exhibited minor variations at the inferomedial angle (Fig. 12b); incidence, 8 specimens. Muscles placed in type II lacked a definite inferomedial angle, thus presenting a rounded border (Fig. 12c); incidence, 3 specimens. Type III includes segmented forms; incidence, 14 specimens. Examples of type IIIa presented a long, V-shaped muscular defect in a low position (Fig. 12d); incidence, 4 specimens. Those of type IIIb exhibited a similar defect in a high position (Fig. 12e); incidence, 3 specimens. Type IIIc included muscles possessing more than one V-shaped defect (Fig. 12f); incidence, 3 specimens. In examples of type IIId the most inferiorly located group of muscle fibers was separated from the main muscle mass and extended inferomedially just above the spermatic cord to a point near the pubic tubercle (Fig.12g); incidence, 4 specimens.

Aponeurotic portion of the transverse abdominal. The aponeurotic portion of the transversus layer lies chiefly in the medial and inferomedial areas of the inguinohypogastric region. The tendinous extensions of the upper transversely directed muscle fibers proceed medialward to their insertions in the linea alba; intermingling with those of the internal oblique, they form the rectus

sheath. Usually they course anteriorly to the rectus muscle in the inguinal region. However, at times some of the fibers may pass posteriorly, and thus form a relatively low linea semicircularis in the upper part of the inguinal region (27, 28). Frequently some of the lower aponeurotic fibers of the transversus may pass posterior to the rectus muscle in gaining attachment in the caudal part of the linea alba and to the body of the pubis. Most commonly the lower aponeurotic fibers of the layer course in a curving direction medialward and caudalward; they fuse with similarly directed fibers of the internal oblique and insert upon the pubis anterior to the rectus muscle. The lowermost aponeurotic fibers frequently assume a more precipitous caudal curve and insert upon the pubis at its spine and lateralward on the pecten as far as the femoral ring. In some instances the fibers pass even farther caudalward, where they fuse with the anterior segment of the fibrous femoral sheath as the descending transversus tendon. Some of the more laterally located fibers of this part of the transversus tendon may insert into the pectineus fascia, into the falciform fascia, or into the deep crural arch as shown by Douglas.

We have not encountered an insertion into the deep crural arch; the transversus layer is not connected to the inner and lower surface of the inguinal ligament.

Actually, the descending aponeurotic fibers of the transversus layer insert into the pecten of the pubis. This means that the insertion can extend only as far as the medial margin of the femoral ring. The fasciae, however, continue caudally to form the anterior part of the fibrous femoral sheath, which also receives a fascial contribution from the lower part of the internal oblique layer (27). Owing to variations in extent and in character of the descending aponeurotic fibers of the transversus, specific names have been given to specialized bands which occur in the layer: when the lateral portion of the aponeurosis is well developed near the medial edge of the abdominal inguinal ring, it has been called the "ligamentum interfoveolar Hesselbachii" by His; a medial portion which lies in close relation to the lateral edge of the rectus sheath has been incorrectly named by His the ligament of Henle.

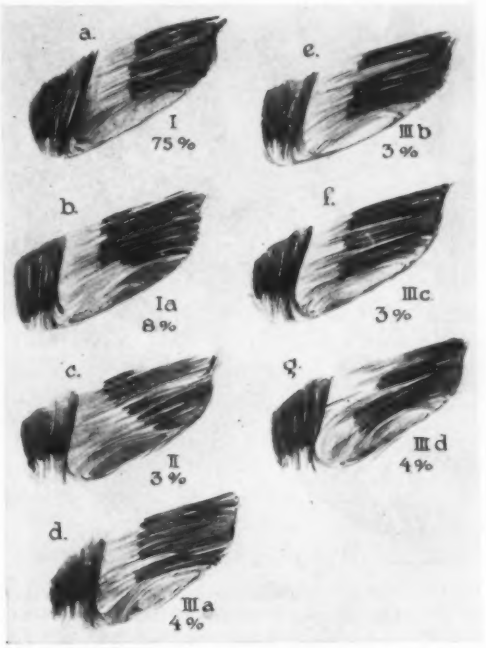


FIG. 12. Transverse abdominal muscle. Posterior (dorsal) aspect. Types encountered in a study of 100 body-halves.

Polya, reviewing the literature on these structures, concludes that the assignment of special names to parts of the same structure is unjustifiable. In general, the observations of the present authors are in agreement with those of Polya.

The transversus aponeurosis was examined in a series of 58 nonhernial body-halves (obtained from 30 adult specimens, 5 females, 25 males) in order to determine its extent and form in the lower part of the inguinal region (Fig. 13).

In 5 specimens (approximately 8 per cent) the aponeurosis failed to extend as far lateralward as the edge of the rectus muscle at its insertion (Fig. 13f).

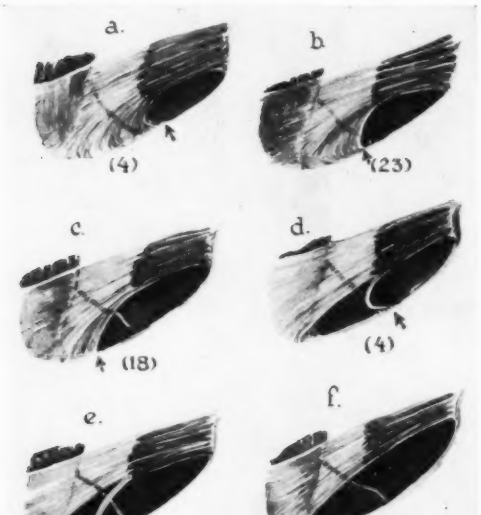


FIG. 13. Transverse abdominal layer. Variation in the extent of its aponeurosis in the inguinal region. Types encountered in a study of 58 body-halves. Arrows indicate aponeurotic attachment to Cooper's ligament.

In 18 specimens (31 per cent) the edge of the ligament lay beyond the edge of the rectus muscle but did not pass a point midway between the lateral edge of the rectus insertion and the point at which the inferior epigastric vessels crossed the inguinal ligament (Fig. 13c).

In 23 (40 per cent) the aponeurosis lay beyond this midpoint but did not extend past the inferior epigastric vessels (Fig. 13b).

In 4 instances (7 per cent) the edge of the aponeurosis extended laterally beyond the point at which the epigastric vessels cross the inguinal ligament, and to the medial margin of the femoral ring (Fig. 13a).

In 8 specimens (14 per cent) a thin band of aponeurotic fibers coursed laterally to the edge of the rectus muscle, leaving an aponeurotic gap between the descending bundle and the main body of the transversus tendon (Fig. 13d and e). This defect was bridged by the transversalis fascia, quite thick in 3 instances, of moderate thickness in 3 specimens, and very thin in 2. The descending bundle of tendinous fibers lay between the edge of the rectus muscle and the inferior epigastric vessels in 4 specimens (Fig. 13e), and in 4 it occurred somewhat lateral to the epigastric vessels—skirting the medial margin of the abdominal inguinal ring and the femoral ring (Fig. 13d).

Polya measured the descending transversus aponeurosis in 50 specimens and found it to vary from 0.5 to 3.5 centimeters in breadth. Blaise found its width to vary from 1.1 to 4.7 centimeters.

Fascial portion of the transversus stratum. The transverse abdominal layer is locally represented by fascia in those instances in which a lunular interval occurs in the area bordered by the caudal margin of the transversus muscle laterally, by the inferolateral edge of the transversus aponeurosis medially, and by the pubic pecten inferiorly. Two fascial layers, fused back-to-back, form this part of the layer, of which the principal contribution is the transversalis fascia. The extent of this unsupported fascial portion of the transversus layer varies reciprocally with the size of the aponeurotic segment of the stratum. The character of the layer also is variable. Quite commonly a localized triangular thickening occurs lateral to the abdominal inguinal ring. Less common is the presence of an area of thickening between the medial margin of the abdominal inguinal ring and the lateral edge of the descending portion of the transversus aponeurosis (Fig. 14).

The occurrence of localized thickenings in the fascial portion of the transversus stratum was studied in 58 body-halves (from 30 adults, 5 females and 25 males). In 16 of 58 (28 per cent) a triangular thickening was encountered lateral to the abdominal inguinal ring in the angle formed by the lower margin of the transversus muscle and the sheath of the iliopsoas muscle (Fig. 14a). In 3 (5 per cent) of these instances the medial edge of the triangular fascial thickening was well defined. In 13 (22 per cent) specimens an area of thickened fascia, in addition to the type described, occurred medial

to the abdominal inguinal ring, between it and the edge of the transversus aponeurosis (Fig. 14b). In the remaining 29 specimens (50 per cent) the entire fascial segment of the transversus aponeurosis was uniform in thickness (Fig. 14c).

APONEUROTIC INGUINAL FALX

Appearing quite consistently in the writings on the subject of inguinohypogastric anatomy are the terms "conjoined tendon" and "aponeurotic inguinal falx." These names have been the source of considerable controversy, down to the present day. Some authors apply one of the two names to that which they regard as one structure; others use the terms interchangeably, according to Eisler; Testut believes that the two names apply to separate structures. Although two famous surgeons, Halsted and Bassini, utilized the conjoined tendon in the operative repair of inguinal hernia, Blake, Bloodgood, Hessert, and Andrews deny the constant presence of the conjoined tendon in well developed form. In our opinion, confusion is the natural result of the wide range of variation in the anatomic constitution of the layers. This matter calls for elucidation.

In the inferomedial area of the inguinohypogastric region, the aponeuroses of the internal oblique and of the transversus layers become intermingled with each other. In the great majority of specimens, fusion occurs close to the edge of the rectus muscle, near the latter's caudal insertion. From this point medialward the two aponeuroses, conjoined, pass anterior to the muscle. In our observations made on nearly 500 body-halves, this fusion did not reach a point more than 2 centimeters lateral to the edge of the rectus muscle. Blake reports comparable findings. In all specimens in which the inferomedial angle of the internal oblique muscle overlies the edge of the rectus muscle, the fusion of the two aponeuroses lies upon the surface of the rectus muscle, simply because the internal oblique aponeurosis, in many instances, does not begin until this point is reached. The fusion of the two

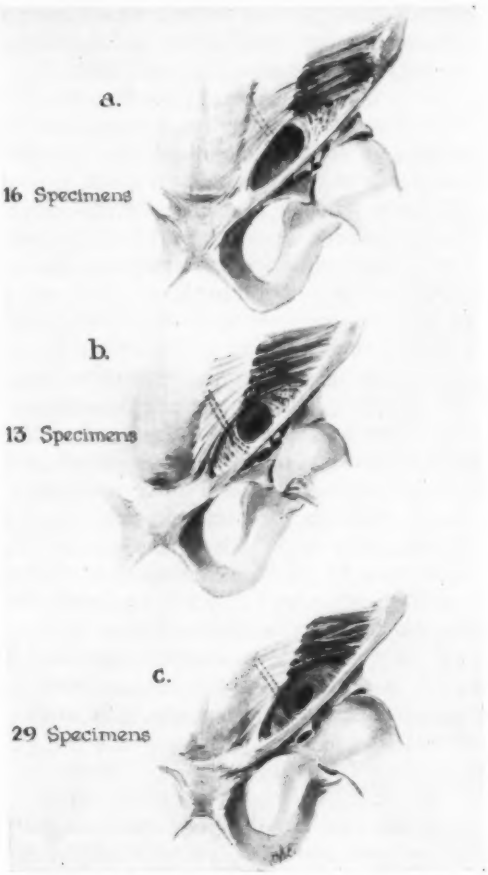


FIG. 14. Transverse abdominal muscle; fascial portion. Types of distribution of a thickened portion of the fascia observed in dissection of 58 inguinal regions.

aponeuroses in the formation of the rectus sheath produces the conjoined tendon as described by Douglas and by Testut. This is the "conjoined tendon" usually referred to in surgical literature. Lateral to the line of fusion of the two aponeuroses the layers are usually quite separate and distinct. It is in this part of the transversus layer that the arciform tendinous fibers may descend to an attachment lateral to the pubic tubercle. Morton included this structure in his description of the conjoined tendon; Testut called it the falx inguinalis, and Eisler includes this structure and the previously de-

scribed fused portion of the internal oblique and transversus aponeuroses in his description of the aponeurotic inguinal falx.

Only in rare instances does the insertion of the internal oblique muscle extend lateral to the pubic tubercle along the superior pubis ramus (in a single instance in our 200 body-halves). The fibers of this inferolaterally directed portion of the aponeurosis arose at a level higher than the caudal margin of the internal oblique layer. Descending in arciform manner to their attachments, they were closely applied to a similar group of fibers in the underlying transversus aponeurosis. Thus, there was present a conjunction of the two aponeuroses, not only in the formation of the anterior rectus sheath, but also in a wide area lateral to the rectus muscle. In this type of anatomic arrangement the conjunction includes the so-called falx inguinalis. In such an instance, the term "conjoined tendon" is perfectly justifiable. On the contrary, when the name includes any part of the transversus aponeurosis which is not fused to the internal oblique aponeurosis, the term is thoroughly unanatomic.

RECTUS TENDON

As an additional aponeurotic support to the inferomedial angle of Hesselbach's area, the caudal attachment of the rectus muscle in some specimens spreads laterally to attach by a broad tendon to the pubis. Sometimes the attachment extends outward upon the pecten of the pubis according to Henle. This lateral expansion of the rectus tendon has been thought by Douglas to be continuous with the descending aponeurotic fibers of the transversus layer, the rectus and the transversus components together then being called "ligament of Henle." This expansion of the rectus tendon, sometimes labeled falx inguinalis, is an entirely different structure from that which is labeled falx inguinalis in anterior view.

Actually, the lateral expansion of the rectus tendon and the aponeurosis of the transversus layer are completely separate and distinct structures. In those instances in which the lower part of the transversus coursed anteriorly to the rectus muscle, the rectus tendon lay dorsal to the transversus layer; and a fascial offshoot, originating from the transversalis fascia, invested both ventral and dorsal surfaces of the rectus muscle. Where aponeurotic fibers of the transversus stratum coursed both anteriorly and posteriorly to the rectus insertion, the lateral expansion of the rectus tendon was found between these two lamellae. In this type of arrangement the rectus fascia originated from the angle of divergence of ensheathing aponeurotic constituents of the transversus (27, 28). In a series of 65 body-halves (33 specimens, 5 females, 28 males) the rectus insertion extended beyond the pubic tubercle in 7 specimens (2 bilaterally, 1 on the left side alone, and 2 on the right). The distance lateral to the pubic tubercle of the edge of this expanded rectus tendon varied as follows: 1.0 to 1.4 centimeters in 3 specimens; 1.5 to 1.9 centimeters in 2; 2.5 centimeters in 1; 3.1 centimeters in 1.

SUBSEROUS LAYER

Lying internal to the transversalis fascia, interposed between it and the peritoneum, is the preperitoneal (retroperitoneal, subserous) layer of connective tissue. Within this layer in the inguinohypogastric region course vascular and visceral structures. Characteristically this lamina is subject to great variation in the lower part of the abdomen. Localized areas in individual specimens may differ quite markedly in composition; and in different subjects, variations may be quite noticeable.

The tissue of the preperitoneal layer may be areolar, adipose, or membranous. In spare subjects the areolar character predominates. Almost constant in all specimens are localized collections of adipose tissue about the blood vessels as they course through the layer. In obese specimens, fatty infiltration of the layer is usually quite noticeable. In many subjects, both lean and obese, parts

of the preperitoneal stratum may be bilaminar in structure, much like the superficial fascia of the lower abdomen, with its outer fatty Camper's layer and inner membranous Scarpa's layer. When this situation exists, the membranous stratum is found external to the fatty or areolar tissue, and closely applied to the surface of the internal investing fascia of the transversus muscle (the transversalis fascia) and to the fascia of the rectus muscle.

Morton, in his discussion of the transversalis fascia, states that the layer is sometimes bilaminar and that the epigastric vessels lie between the two laminae. Zieman speaks of a layer which he calls transversalis fascia. According to him this layer " . . . is entirely aponeurotic, lies beneath all the above mentioned structures (the three muscular layers of the abdomen), and has connection with the transversus abdominis muscle only by contiguity." The membranous preperitoneal layer can be dissected away from the internal surface of the abdominal wall, leaving an inner fascial investment upon the transversus muscle and aponeurosis. This fascial layer is continuous where the musculoaponeurotic segments of the transversus are deficient. The membranous preperitoneal layer gradually decreases in thickness as it is traced cranialward, lateralward, and dorsalward, finally to disappear as it leaves the area of the inguinohypogastric region. The consistency of the membranous preperitoneal layer is less dense than that of the layer investing the inner surface of the transversus muscle. In hernial specimens in which the layers are well developed, a funicular investment has been found that originates at the abdominal inguinal ring from the fascial part of the transversus layer. A deeper funicular layer has been traced to the membranous stratum of the preperitoneal layer.

The layer which in early descriptions was called "transversalis fascia" is doubtless the preperitoneal layer (tela subserosa). Its membranous character in spare subjects (as seen at the operating table) accounts for much of the confusion prevalent today in surgical circles regarding its constitution and continuities. Identification of the true transversalis fascia is important, because the transversus stratum, which includes the transversalis fascia, is the dependable layer in the repair of the groin hernias. The preperitoneal layer, on the contrary, is worthless in hernial repair; because it consists of a loosely woven layer of areolar fibers, this subserous stratum has virtually no tensile strength.

CONSTITUTION OF THE INGUINAL WALL IN THE AREA OF HESSELBACH'S TRIANGLE

It has been established in the foregoing sections that numerous variations occur in the superimposed strata which form the wall of the inguinal region; and it has been demonstrated that certain of the variants in the layers are structural deficiencies due to weakness. The combined relationship of such attenuation in the layers of a given inguinohypogastric region determines the capacity of a particular area of the parietes to withstand herniation.

Where there is no developmental basis for a preformed sac (of a persistent patent processus vaginalis), it is our belief that the anatomic constitution of the abdominal wall in the triangle of Hesselbach is the primary factor which determines resistance to direct herniation. We also believe that there are two types of supporting layers in this region of the abdominal wall: those physiologically active—the musculoaponeurotic segments of the transversus, internal oblique and external oblique—and those which are physiologically inert—peritoneum, preperitoneal layer, and the bilaminar fascial layers which complete distally the three musculoaponeurotic sheaths. We hold, as do Keith, Zimmerman, and Cherner, that the more important of the two types of supporting layers are the physiologically active musculoaponeurotic sheets. Certain investigators have further selected a single stratum as the most important. Hill, Milch, and Pitzman maintain that the transversus stratum is the most effective barrier against direct herniation and in this opinion we concur. Others be-

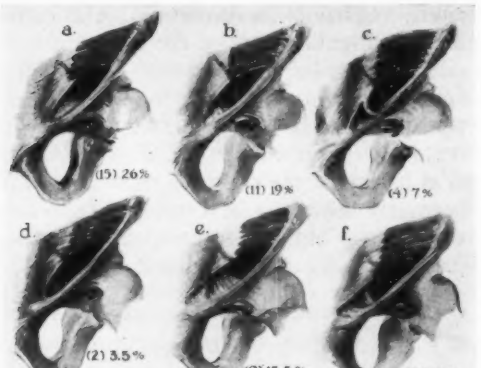


FIG. 15. Internal oblique and transverse abdominal layers. Variation in the combined aponeurotic contribution to the area of the triangle of Hesselbach in 58 dissections.

lieve that the internal oblique serves in this important capacity.

In this connection it is important to note that the musculoaponeurotic sheath of the internal oblique, when its lower fibers are attached to the pubis as far laterally as the edge of the rectus muscle, is mechanically capable of shutter-like action; but when its inferomedial insertion is more cranially placed (presence of an inguinal triangle), such action is mechanically impossible (and the inferomedial part of Hesselbach's triangle is lacking in aponeurotic fibers in the internal oblique layer). Because this is the most common major defect in the area of Hesselbach's triangle, the musculoaponeurotic portions of the internal oblique and transversus strata were used as a basis for the following observations (Fig. 15).

In order to clarify this matter, 58 body-halves were studied—10 female, from 5 cadavers; 48 male, from 26 cadavers. In 15 of 58 cases (26 per cent) both internal oblique and transversus layers were completely musculoaponeurotic in Hesselbach's triangle (Fig. 15a). In 2 instances an expansion of the caudal rectus tendon added to the musculoaponeurotic support. Thus, 2 or more physiologically active strata supported the area of direct hernia.

In 11 body-halves (19 per cent) there was a completely musculoaponeurotic internal oblique in the presence of a transversus tendon which extended only half the distance across Hesselbach's triangle (Fig. 15b).

In 4 specimens (7 per cent) possessing complete internal oblique aponeuroses, a small bundle of transversus aponeurotic fibers (incompletely aponeurotic) descended through Hesselbach's triangle (Fig. 15c).

In 2 instances (3.5 per cent) no musculoaponeurotic support was given to the lower area of Hesselbach's triangle by the transversus stratum. In 1 the internal oblique was the only musculoaponeurotic element; in the other, a well developed lateral expansion of the rectus tendon was present in addition to the internal oblique (Fig. 15d).

In 9 cases (15.5 per cent) the musculoaponeurotic segment of the internal oblique was defective, but the musculoaponeurotic transversus stratum was complete. Two were reinforced by a lateral expansion of the rectus tendon (Fig. 15e).

In 10 body-halves with deficient internal oblique (17 per cent) the descending transversus tendon extended only halfway across the triangle of Hesselbach. The fascial part of the transversus stratum in the lower area of Hesselbach's triangle was quite heavy in 3 of these specimens (Fig. 15f).

In 4 instances (7 per cent) in which the internal oblique was defective, the only aponeurotic representation was a small bundle of transversus aponeurotic fibers. In but 1 of these the intervening fascial part of the transversus was thickened (Fig. 15g).

In 3 of the body-halves (5 per cent) neither the internal oblique nor the transversus gave support to the triangle of Hesselbach. However, in 2 there occurred a lateral expansion of the rectus tendon—in-

effective as a barrier owing to its small size; and in 1 the fascial part of the transversus was quite heavy (Fig. 15h). These specimens had no physiologically active layer to support the area in Hesselbach's triangle except the crura of the aponeurotic cleft in the external oblique layer. In this small area, outlined by the aponeurotic cleft, the sole support to the area of direct hernia consisted of the superimposed inert layers of the wall. It is in this type of structure that the size of the aponeurotic cleft determines the area of inguinal wall which is devoid of aponeurosis.

From these observations it is evident that in 7 (12 per cent) of 58 specimens examined, musculoaponeurotic support to the lower part of Hesselbach's triangle, both from internal oblique and from transversus strata, was either totally absent or very poorly developed (Fig. 15g and h); in 62 per cent the musculoaponeurotic portion of one of the two layers was either partly or completely defective (Fig. 15b to f); and only in the remaining 26 per cent of instances was the area of direct hernia completely supported by physiologically active musculoaponeurotic segments of both layers (Fig. 15a).

Some surgeons have stressed the use of transversalis fascia in the repair of a direct inguinal hernia. Seelig and Chouke have stated that they have been unable to find the so-called transversalis fascia. By some individuals this term is used in a broad sense, signifying the descending transversus tendon together with its investing fascia. Still others mistakenly apply the name to the preperitoneal connective tissue. In the foregoing studies of the transversus layer, it has been demonstrated that the descending portion of the transversus aponeurosis failed to extend lateral to the edge of the rectus muscle in 5 of 58 body-halves (less than 9 per cent), and that nothing more than a small bundle of aponeurotic fibers entered Hesselbach's triangle in an additional 8 cases (approximately 14 per cent). The entire fascial portion of the transversus stratum was found to be quite thin in 29 of 58 body-halves (50 per cent) and thickened in its medial portion in only 13 (approximately 22 per cent). In 13 specimens in which the transversus aponeurosis was either absent or poorly developed between the abdominal ring and the rectus muscle, the defect in the aponeurosis was compensated for by fascial thickening in 2 specimens, by a lateral expansion of the rectus tendon in 2, and by both in 1.

Thus, in 5 of 58 body-halves (8 per cent) the portion of the transversus stratum between the abdominal inguinal ring and the edge of the rectus muscle was merely an attenuated fascial layer which could not be useful in hernial repair. It seems likely that the individuals who express difficulty in finding the transversalis fascia have encountered specimens of this type.

In the combined study of internal oblique and transversus strata in 58 specimens there were 5 (approximately 8 per cent) which exhibited not only structural features which would prevent the shutter, or arcade, action of internal oblique and transversus muscles, but also lack of surgically useful tissue (absence of muscle, absence or deficiency of aponeurosis, lack of thickened fascia) in the inguinal triangle caudal to the lower margin of the internal oblique muscle (Fig. 15g and h). Perhaps in this anatomic observation lies the explanation for direct recurrence in cases of simple, uncomplicated, indirect inguinal hernioplasty. In this group of specimens, 9 per cent presented no musculoaponeurotic barrier to direct herniation; this incidence rather closely parallels the average recurrence rate in many large series of hernia operations, predominantly of the indirect variety.

SUMMARY AND CONCLUSIONS

For the purpose of eliminating confusion and inaccuracies created by conventionalized inguinal anatomy, and for the purpose of demonstrating variations in the inguinohypogastric structures, a study was conducted of 500 body-halves—with emphasis on the parietal layers which support the region of inguinal hernia.

In the inguinohypogastric region the external oblique layer is, with rare exceptions, aponeurotic in structure. Contained in the stratum is the aponeurotic cleft, a fusiform gap formed by separation of aponeurotic fibers to allow the spermatic cord to pass through the layer. Wide variation is found in the length and breadth of the cleft, but departure from its fusiform shape with its inferomedial apex lying over the pubic symphysis is rarely observed. The superolateral angle of the cleft was found to lie within the limits of Hesselbach's triangle in 63 per cent of 65 body-halves and superolateral to the inferior epigastric artery in 37 per cent. Intercrural fibers, when present, are almost invariably confined to the external investing fascia of the external oblique stratum—the fascia innominata. They were found in 54 per cent of 200 specimens. In all specimens examined, a reflected inguinal ligament was present, formed by fan-shaped spread of fibers of the inguinal ligament in medial and cranial directions from the pubic tubercle into the plane of the internal oblique layer. Another structure to which the name reflected inguinal ligament is applied, formed by extension of the superior crus of the aponeurotic cleft across the midline to an insertion at the pubic tubercle of the opposite side, occurred in only 5 of 250 body-halves by Anson and McVay (2, 3).

In approximately 75 per cent of inguinal regions the internal oblique layer is composed mainly of muscle. The chief variation in this stratum is the site of attachment of the internal oblique aponeurosis. In approximately 37 per cent of 500 specimens the lower border of the internal oblique aponeurosis at the edge of the rectus muscle failed to reach as far caudally as the level of the pubic tubercle. It is in this type of inguinal region that a so-called "inguinal triangle" exists. When the medial tendinous attachment of the internal oblique muscle is thus located, the arcade or shutter action of the muscle is limited or impossible. A second variant in the internal oblique stratum is a fusiform musculoaponeurotic defect, often filled by adipose tissue and crossed by the investing fasciae of the layer. Defects of this type were found in approximately 22 per cent of 500 specimens. Herniation through such defects had been observed clinically.

Occurring between internal oblique and transversus strata in the inguinal region is a band of musculature called the accessory internal oblique muscle. In a series of 218 body-halves it was found in 73 (33.5 per cent). The role played by this muscle in the support of the groin against herniation depends upon its caudal extent. In 3 per cent of the cases this muscular band lay caudal to both internal oblique and transversus layers. In that position it served as the only musculoaponeurotic support to the superolateral region of the inguinal canal.

By far the most variable layer in the inguinal region is the transversus stratum. Muscle fibers of the transverse abdominal descended more than half the distance into the inguinal region—from a line connecting the anterior iliac spines—in only 24.5 per cent of 404 cases. Fusiform musculoaponeurotic defects were found in 13 per cent of 100 specimens examined. Despite rather marked differences in quantity of muscle, the major variation in the transversus layer is the form and attachments of its aponeurosis, the lower border of which may be found to vary from a relatively high position in the rectus sheath to a position at the medial margin of the femoral ring. In 8 of 58 specimens examined (14 per cent) nothing more substantial than a thin band of aponeurotic fibers entered the triangle of Hesselbach. Where muscle and aponeurosis are lacking in the transversus layer, continuity is maintained by the fused investing fasciae of the musculoaponeurotic segments, the internal of which is called the transversalis fascia. Among 58 body-halves examined there were fascial thickenings lying medial to the internal inguinal ring in 13 (22 per cent) and lateral to the ring in 16 specimens (28 per cent).

Quite distinct from the aponeurosis of the transversus layer is the tendon of insertion

of the rectus muscle. In 7 of 65 body-halves (approximately 10 per cent) it extended lateralward in the form of a fan, beyond the pubic tubercle to an attachment on the pubic pecten. This structure is the ligament of Henle—incorrectly termed "falx inguinalis." Only when large and well developed could this ligament serve as musculoaponeurotic support to the triangle of Hesselbach.

In the combined study of internal oblique and transverse abdominal layers, 5 in 58 body-halves (8 per cent) exhibited not only structural features which would preclude the shutter or arcade action, but also surgically useless tissue—that is, lacking muscle, aponeurosis or thickened fascia—in the inguinal triangle caudal to the lower margin of the internal oblique muscle. We believe that herein lies the explanation for a direct recurrence following a simple, uncomplicated, indirect inguinal herniorrhaphy.

REFERENCES

1. Andrews, E. A method of herniotomy utilizing only white fascia. Ann. Surg., 1924, 80: 225–238.
2. Anson, B. J. An Atlas of Human Anatomy. Philadelphia: W. B. Saunders Co., 1950.
3. Anson, B. J., and McVay, C. B. Inguinal hernia; the anatomy of the region. Surg. Gyn. Obst., 1938, 66: 186–191.
4. Idem. The anatomy of the inguinal and hypogastric regions of the abdominal wall. Anat. Rec., 1938, 70: 211–225.
5. Bassini, E. Ueber die Behandlung des Leistenbruches. Arch. klin. Chir., 1890, 40: 429–476.
6. Blaise, P. Canal inguinal chez l'adulte. Cure radicale de la hernie inguinale. Paris. (Procede de M. Paul Berger). g. Steinheil, 1894.
7. Blake, J. A. The relative bearing of the conjoined tendon and the internal oblique muscle upon the radical cure of inguinal hernia. Med. Rec., N. Y., 1900, 58: 321–324.
8. Bloodgood, J. C. Operation in 459 cases of hernia. Rep. Johns Hopkins Hosp., 1899, 7: 223–562.
9. Camper, P. Sämmtliche Kleinere Schriften. Vol. II, p. 50. Leipzig: S. L. Crusius. 1785.
10. Chandler, S. B., and Schadewald, M. Studies of inguinal region; conjoined aponeurosis versus conjoined tendon. Anat. Rec., 1944, 89: 339–343.
11. Cherner, M. Indirect inguinal hernia in the light of the newer interpretation of anatomy. Ann. Surg., 1934, 99: 577–584.
12. Chouke, K. S. Composition of the sheath of the rectus muscle. Anat. Rec., 1935, 61: 341–349.
13. Cloquet, J. Recherches anatomiques sur les hernies de l'abdomen. Paris, These, 1817.
14. Cooper, Sir Astley. The anatomy and surgical treatment of abdominal hernia. In two parts, 2nd ed. by C. A. Key. London: Longman, Rees, Orme, Brown and Green, 1827.
15. Cruveilhier, J. Traite d'anatomie pathologique generale. Paris: Bailliere, 1849.
16. Douglas, K. M. Fat hernia in the inguinal region. Edinburgh M. J., 1889–1890, 35: 918–921.
17. Eisler, P. The rectus muscle and its sheath. Verh. Anat. Ges., 1898.
18. Gallaudet, B. B. A Description of the Planes of Fascia of the Human Body. New York: Columbia University Press, 1931.
19. Halsted, W. S. The cure of the more difficult as well as the simpler inguinal ruptures. Bull. Johns Hopkins Hosp., 1903, 14: 208–214.
20. Henle, J. Handbuch der Muskellehre des Menschen. Braunschweiz: Friedrich Vieweg und Sohn, 1871.
21. Hesselbach, F. C. Neueste Anatomisch-pathologische untersuchungen ueber den Ursprung und das Fortschreiten der Lestern- und Schenkelbruche. Wurzburg: J. Stahel, 1814.
22. Hessert, W. Recurrences following operations for inguinal hernia. Surg. Gyn. Obst., 1922, 35: 431–436.
23. Hill, L. V. Some anatomical studies in oblique inguinal hernia. J. Kansas M. Soc., 1932. 33: 75–77.
24. His, W. Die anatomische Nomenklatur. Arch. Ana. Physiol., 1895, suppl. vol.
25. Keith, Sir Arthur. On the origin and nature of hernia. Brit. J. Surg., 1924, 11: 455–475.
26. McVay, C. B., and Anson, B. J. Fascial continuities in the abdominal, perineal, and femoral regions. Anat. Rec., 1938, 71: 401–407.
27. Idem. Aponeurotic and fascial continuities in the abdomen, pelvis, and thigh. Anat. Rec., 1940, 76: 213–224.
28. Idem. Composition of the rectus sheath. Anat. Rec., 1940, 77: 213–225.
29. Milch, H. Transversalis fascia in inguinal hernioplasty. Med. Rec., N. Y., 1935, 1942: 397–398.
30. Morton, T. The Surgical Anatomy of Inguinal Herniae, the Testis and Its Coverings. London: Taylor and Walton, 1841.
31. Pitzman, M. A fundamentally new technic for inguinal herniotomy. Ann. Surg., 1921, 74: 610–619.
32. Polya, E. Die Ursachen der recidive nach radicaloperation des Leistenbruches. Arch. klin. Chir., 1912, 99: 816–877.
33. Scarpa, A. A Treatise on Hernia. Transl. by J. H. Wishart. Edinburgh: T. Bryce & Co., 1814.
34. Seelig, M. G., and Chouke, K. S. A fundamental factor in the recurrence of inguinal hernia. Arch. Surg., 1923, 7: 553–572.
35. Testut, L. Traite d'anatomie humaine. Vol. I. Paris: O. Doin, 1921.
36. Zieman, S. A. The diagnosis of hernia. J. Am. M. Ass., 1940, 115: 1873–1874.
37. Zimmerman, L. M. Surgical treatment of direct inguinal hernia. Surg. Gyn. Obst., 1938, 66: 192–198.

COMPLICATIONS OF COLOTOMY AND POLYPECTOMY

GEORGE KLEINFELD, M.D., and FRANK E. GUMP, M.D., New York, New York

BECAUSE OF THE POTENTIAL for malignancy in polyps of the colon, there is currently prevalent among surgeons the viewpoint that colonic polyps, once diagnosed, should be excised. Supporting this viewpoint is the contention that simple laparotomy with colotomy and polypectomy carries little risk of postoperative morbidity. In fact, Bacon and Dedish recommend that several colotomy incisions be made to allow inspection of the entire colon through the sigmoidoscope. In contrast to this general impression of the simplicity of the postoperative course, however, Dedish reports a surprisingly high incidence of complications. Furthermore, published evidence of the supposed small incidence of postoperative difficulties is lacking.

In order to analyze further the risks of colotomy and polypectomy, a series of such cases from the Columbia-Presbyterian Medical Center between the years 1943 to 1959 were reviewed. Both ward and private patients were considered. There were 18 children less than 12 years of age; their cases received separate consideration.

In the majority of patients, the bowel was prepared for operation by a combination of mechanical cleansing and orally administered antibiotics (160 cases). Less frequently used were antibiotic preparation alone (80 cases), mechanical preparation alone (44 cases), and no significant preparation (27 cases). Thalamyd and bacitracin-neomycin were the antibiotics most often used, with neomycin and other agents given relatively infrequently. We defined an antibiotic bowel preparation as the oral administration of a poorly absorbed antibiotic for a period of at least 24 hours prior to operation. It was somewhat more difficult to decide what should be considered adequate mechanical preparation of the bowel since every patient had at least an enema before operation was undertaken. No patients were considered as having had mechanical bowel preparation unless the following criteria were met: (1) one or more doses of castor oil, (2) multiple enemas, and (3) at least 2 days of a diet limited to fluids.

The sigmoid was the site of colotomy in 231 patients, the descending colon in 56 patients, the transverse colon in 44 patients, the ascending colon and cecum in 22 patients, and in 9 patients, the colotomy was made in one of the flexures. In 60 patients more than 1 colotomy was performed.

The predominant pathologic diagnosis was adenomatous polyp, noted in 256 cases. There were 16 cases of adenomatous polyps with intramucosal carcinoma, and 17 with invasive carcinoma in the tuft. There were 17 instances of papillary adenomas, 5 of which contained invasive carcinoma. In 11 cases no polyp was found; in 1 case an appendix stump was noted; in 1 instance the finding was an intramural lipoma, and in another instance a leiomyoma.

Sigmoidoscopy through one or more colotomies was performed at the time of operation in 149 of the 311 patients. In some instances, the sigmoidoscope was employed in order to find the polyp, whereas in other patients it was used to rule out additional polyps that might have been missed by palpation alone.

The most frequently used colotomy technique consisted of a longitudinal incision closed in the same axis by a row of absorbable sutures followed by an inverting layer of seromuscular silk sutures. Less often used was a longitudinal colotomy incision closed transversely, and rarely used was a trans-

From the Department of Surgery, Presbyterian Hospital and the College of Physicians and Surgeons, Columbia University, New York.

verse colotomy incision closed transversely.

Postoperative antibiotics were administered to 252 of the 311 patients for a minimum of 5 days. Penicillin and streptomycin were given to 204 patients while the remaining 48 received a broad spectrum antibiotic.

A total of 81 complications developed postoperatively in 61 patients, a patient complication rate of 20 per cent. Included were pneumonia, thrombophlebitis, myocardial infarction, and other problems more closely related to anesthesia and laparotomy than to the performance of a colotomy. On the other hand, the patient complication rate for the group in which the problems were directly related to the colotomy was 14 per cent. This group included 19 instances of wound infection (6 per cent), 12 of abscesses and fistulas (4 per cent), 10 of bleeding (3 per cent), and 9 of ileus (3 per cent). The wound infections were all superficial and cultures grew out Escherichia coli 7 times, Staphylococcus aureus, coagulase positive, 4 times, while in the remaining 5 infections mixed coliform organisms were encountered. Twelve paracolic abscesses and fecal fistulas were thought to represent leakage or breakdown of the colotomy wound. Eight of the patients bled per rectum but in only 3 instances was it severe enough to require transfusion. The remaining 2 bleeding episodes were retroperitoneal extravasations following mobilization of the colon prior to colotomy. All of the 9 patients in whom intestinal obstruction developed in the immediate postoperative period were treated by Miller-Abbott tube decompression. In 2 patients, however, laparotomy with lysis of adhesions was necessary.

Twenty-three reparative operations were performed in this series. Six patients required resuture of disrupted wounds. Three diverting colostomies were performed for treatment of colotomy leakage or fistulas. In 3 patients chronic fistulas developed that had to be excised, and 3 more patients required drainage of pelvic collections. A cecostomy was necessary in 1 patient because obstruction developed at the colotomy. Another patient required re-exploration to oversew a bleeding point at the site of the polypectomy. Chronically infected silk sinus tracts had to be excised in 3 patients. The 2 patients who required lysis of adhesions were mentioned previously. One patient was re-explored 9 months after polypectomy for a mass which was found to be a granuloma of the bowel wall secondary to the previous colotomy. Only 4 fatalities occurred in this series; these were in poor risk patients whose deaths were not due to complications of the colotomy itself.

The cases in which wound infections developed were analyzed in an effort to discover what factors, if any, might be responsible for the high infection rate. The type of bowel preparation, the use of postoperative antibiotics, and the use of the sigmoidoscope were considered. By a chi square analysis, no significant differences were found except in the use of the sigmoidoscope. The wound infection rate was 3 times as great in the patients in whom sigmoidoscopy was performed through colotomy incisions. Analysis revealed that this difference had only a 2 per cent chance of being due to chance alone ($X^2 = 5.39$, $p = .02$).

The paracolic abscesses and fistulas were studied in a similar fashion. Once again, the only significant difference appeared in the use of the sigmoidoscope. In this case there was only a 1 per cent possibility that the difference was due to chance alone ($X^2 = 10.07$, $p = .01$). Although the patients who had antibiotic bowel preparation had a 1.2 per cent incidence of abscess or fistula as compared to the 3.7 per cent seen in patients with both antibiotic and mechanical preparation, this difference is not significant ($X^2 = .118$, $p = .73$). In a similar fashion, the use of postoperative antibiotics caused no significant change in the percentage of abscess or fistula formation ($X^2 = .372$, $p = .55$).

Transabdominal polypectomies were carried out in 18 children between the ages of 18 months and 11 years. All of the lesions

were benign polyps with no evidence of carcinoma. No complications occurred in this group.

DISCUSSION

The complication rate of 20 per cent in this series of cases is obviously quite high. It should be noted that minor febrile reactions and transient urinary, pulmonary, or other difficulties were not recorded. Furthermore, a number of patients sustained multiple complications which are not reflected in the percentage figure. The very serious nature of some of these complications is suggested by the 7 per cent incidence of reparative operations, some of these going on to several procedures and producing months of disability. Dedish reports a similarly high complication rate in 106 patients even if the 18 cases he designated mild peritonitis (transient, low grade postoperative fever) are not considered.

Analysis of the complicated cases in our series with respect to the number of colotomies, location of colotomies, type of colotomy closure, and the use of the sigmoidoscope implicates only the sigmoidoscope as a cause of wound and intraperitoneal infection and colotomy breakdown. It is striking to note that all of the intraperitoneal abscesses and fecal fistulas developed in patients who had had a sigmoidoscopy. Of corollary interest is the failure of antibiotics, both in the bowel preparation and in the immediate postoperative period, to alter significantly the wound infection and colotomy breakdown rates.

It seems reasonable to conclude from this review that when the sigmoidoscope is used in connection with colotomy and polypectomy, there is a significant risk of postoperative morbidity. Judgment should be employed in the selection of cases for operation. As shown by Grinnell and Lane, the incidence of carcinoma is less than 1 per cent if the polyp tuft is less than 1 centimeter in diameter. They also emphasize the infrequency of metastases when a stalk is present. Consequently, it appears quite safe to defer operation when there is roentgenographic evidence of a stalked polyp less than 1 centimeter in size, provided that adequate follow-up examinations are possible. At operation, if one desires to minimize the frequency of postoperative difficulties, the colon should be examined and the polyp located by careful palpation. On the basis of the previously mentioned infrequency of carcinoma in small polyps, certainly those polyps which are not detectable by palpation of the colon and require endoscopy to discover are of little significance in terms of cancer detection. If more than 1 polyp is present removal is safer through appropriate colotomies than through a single colotomy incision via the sigmoidoscope.

CONCLUSIONS

Colotomy and polypectomy in which the sigmoidoscope is used entail significant risk of postoperative morbidity. Judgment should be employed in the selection of cases for operation.

REFERENCES

1. Bacon, H. E., and Peale, A. R. Appraisal of adenomatous polyps of the colon, their histopathology and surgical management. Ann. Surg., 1956, 144: 9-18.
2. Dedish, M. R., and Hertz, R. E. Colotomy and coloscopy in the management of mucosal polyps and cancer of the colon. Am. J. Surg., 1955, 90: 846-849.
3. Grinnell, R. S., and Lane, N. Benign and malignant adenomatous polyps and papillary adenomas of the colon and rectum; an analysis of 1,856 tumors in 1,335 patients. Surg. Gyn. Obst., Internat. Abstr. Surg., 1958, 106: 519-538.

USE OF PACKED RED CELLS VERSUS WHOLE BLOOD IN THE PRESENCE OF IMPAIRED CARDIAC RESERVE

MARTIN L. DALTON, JR., M.D., HENRY TYLER, B.S., and
JAMES D. HARDY, M.D., F.A.C.S., Jackson, Mississippi

A TREND toward the use of packed red cells in lieu of whole blood in the treatment of the elderly oligemic patient has become even more marked in recent years. This is particularly true in the rather special case of the elderly patient with an impaired cardiac reserve, according to Gibson (2). This therapeutic rationale is well founded and based principally upon the following contentions. First, it has been recognized for many years that total blood volume may be increased in the presence of congestive heart failure, frequently by as much as 55 per cent or more in Gibson's investigations (1). The second point, a corollary to the first, is that the reduced volume of the packed cells is less likely to cause hypervolemia or to aggravate pre-existing hypervolemia, with the possible production of acute pulmonary edema.

Some years ago experiments were conducted (4) which indicated that the transfusion of the anemic patient with whole blood at times increased the total blood volume by little more than the volume of the infused red cells. Therefore, the primary objective of this study was to undertake a physiologic comparison of infusions of equivalent amounts of whole blood and packed red cells with respect to red cell mass. To simulate conditions of clinical heart failure, large arteriovenous fistulas were created in dogs. A secondary objective was to re-examine the incidence of bacteremia in the presence of large arteriovenous fistulas in these animals.

From the Department of Surgery, University of Mississippi Medical Center, Jackson.
Supported by Army Contract No. DA-49-007-MD-627.

METHODS AND PROCEDURE

Thirty-five apparently healthy adult mongrel dogs weighing an average of 15 kilograms were used in this series of experiments. Utilizing intravenous pentobarbital anesthesia and routine sterile technique, a 1 centimeter side to side aorticocaval fistula was created midway between the renal vessels and the aortic bifurcation. At the completion of the procedure 600,000 units of procaine penicillin were given intramuscularly. This dose was repeated twice weekly thereafter and the dogs were weighed weekly. Blood cultures were obtained aseptically at biweekly intervals. Otherwise, the animals were fed routine dog ration and received no special care. Fifteen of the original animals died prior to reaching the chronic phase of congestive heart failure, and these deaths usually could be attributed to the effects of acute congestive heart failure.

Twenty dogs reached the chronic phase of cardiac decompensation, usually 3 to 6 weeks after creation of the aorticocaval fistula. When adjudged to be in frank chronic congestive heart failure, the dogs were transfused with either 1,000 milliliters of whole blood or 500 milliliters of packed red cells. All blood used for transfusion was obtained aseptically and freshly administered. To improve statistical validity, whole blood was given first to 1 dog and packed red cells first to the next. Each dog served as his own control by receiving the alternate infusion approximately 2 weeks after the first. Twelve of the dogs in chronic failure were transfused at separate times with both packed red cells and whole blood; 4 were transfused with

TABLE I.—COMPARISON OF BLOOD VOLUME BEFORE AND AFTER ADMINISTRATION OF 500 CUBIC CENTIMETERS OF PACKED RED CELLS AND 1,000 CUBIC CENTIMETERS OF WHOLE BLOOD

Dog. No.	Whole blood RCV Before	Whole blood RCV After	Whole blood PV B	Whole blood PV A	Whole blood TBV B	Whole blood TBV A	Packed red cells RCV B	Packed red cells RCV A	Packed red cells PV B	Packed red cells PV A	Packed red cells TBV B	Packed red cells TBV A
1 2-48(a)	719	1330	1600	1822	2319	3152	Hemolyzed					
2 2-40	687	687	940	1066	1627	1753	509	819	1150	1245	1659	2064
3 1-47(a)	611	931	1086	1602	1697	2533	819	1402	1245	1348	2064	2750
4 2-47	1040	2080	2050	2589	3090	4669	Hemolyzed					
5 1-44	577	843	1025	1329	1602	2172	422	1180	1587	1469	2009	2649
6 2-45	638	1096	1386	1893	2024	2989	382	848	1294	1348	1676	2196
7 1-47(b)	538	697	827	994	1365	1691	334	923	871	879	1205	1802
8 2-46(a)	353	672	919	1025	1272	1697	Hemolyzed					
9 1-46(a)	494	903	1049	1367	1543	2270	675	1241	911	848	1586	2089
10 2-46(b)	401	952	827	1185	1228	2137	454	972	820	729	1274	1701
11 2-42	540	1020	1150	1409	1690	2429	600	1200	1188	1180	1790	2370
12 2-43	558	1028	1100	1449	1658	2477	Hemolyzed					
13 1-41(a)	435	941	708	1171	1143	2112	Died					
14 2-48(b)	396	1025	1367	1538	1763	2563	Died					
15 2-41	489	994	911	994	1400	1988	Died					
16 1-41(b)	298	1180	1058	1468	1356	2648	Died					
17 1-59		Died					853	1508	1227	1125	2080	2633
18 1-46(b)		Died					782	1656	1277	1265	2059	2921
19 2-44		Died					835	1592	1833	1727	2668	3319
20 1-92		Died					578	1082	968	959	1546	2041
Mean	549	1024	1125	1429	1674	2453	604	1202	1190	1177	1794	2379

Some samples were too hemolyzed to interpret colorimetrically. Twelve animals were given each type of infusion; 4 received packed red cells only; and 4 received whole blood only prior to death.

packed red cells only; and 4 were transfused prior to their death with whole blood only.

The animals were lightly anesthetized with intravenous pentobarbital, and all transfusions were administered via a cannulated femoral vein in 1 hour's time. The right atrial pressure, femoral arterial pressure, pulse rate, and respiratory rate were measured frequently before, during, and for 1 hour after each transfusion. The hematocrit, total plasma proteins, plasma volume utilizing Evans' blue dye, and total blood volume were measured before and immediately after each transfusion. The error of the Evans' blue dye-hematocrit blood volume measurement is in the range of 10 per cent.

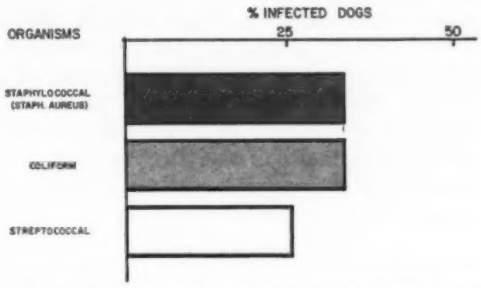
Two normal control dogs were lightly anesthetized in a similar manner and connected to all of the recording instruments. Each animal received 1,000 milliliters of whole blood and similar measurements were recorded before, during, and after transfusion.

RESULTS

Evidence of cardiac failure. Weight gain was a constant feature of the 20 dogs in chronic failure, the onset occurring about 15 days after creation of the fistula. The average weight gain was 3.3 kilograms over the 4 to 12 week period of observation. Extremely rapid weight gain was soon noted to be a poor prognostic sign, since these animals only rarely lived longer than 1 week after operation. However, increasing weight gain in the presence of a continuous abdominal murmur was taken to be indicative of a fistula effectively producing cardiac decompensation. In the majority of these dogs in chronic failure, pitting edema of the rear extremities and ascites to a varying degree also developed.

Physiologic effects of transfusions. The physiologic response to the insult of transfusion in a dog in severe cardiac decompensation varied greatly. The entire range of response was elicited, varying from no detectable change to death during or soon after a transfusion. However, in general, the recorded response to each type of infusion was much less than that expected.

The cardiac rate and the femoral arterial pressure remained essentially unchanged during and after transfusion in each instance, as compared to the pretransfusion level, while the animal was under general anesthesia. The respiratory rate increased an average of 5 per minute after both the whole blood and the packed red cell infusions, but here, of course, it was impossible to exclude the effect of a general anesthetic. The right atrial pressure afforded the most striking contrast between the two types of transfusion. After administration of 500 milliliters of packed red cells the atrial



1. Incidence of positive blood cultures in the dogs with chronic cardiac decompensation induced by aorticocaval fistula. Persistent bacteremia occurred in 67 per cent of these animals.

pressure rose only 13 per cent, as recorded 30 minutes after completion of the infusion. After administration of 1,000 milliliters of whole blood, however, this pressure rose an average of 21 per cent above the pretransfusion level. The right atrial prssure of the normal control dogs increased 15 per cent during the administration of 1,000 milliliters of whole blood but returned to pretransfusion levels within 15 minutes after completion of the transfusion.

Changes in plasma volume and red cell mass (Table 1). The plasma volume of the dogs transfused with 1,000 milliliters of whole blood increased an average of 317 milliliters with little variation from this mean value. The red cell mass increased an average of 20 per cent more in the dogs receiving 500 milliliters of packed red cells than in those receiving 1,000 milliliters of whole blood. The significance of this finding is uncertain. The total blood volume, calculated from the plasma volume and the hematocrit values, was increased by an average value of 24 per cent in the animals given whole blood, as compared to those receiving 500 milliliters of packed red cells ($p > .001$). The total plasma proteins were increased after transfusion with each medium, but the difference was not statistically significant, as had been anticipated.

Incidence of bacteremia. Bacteremia, studied by routine blood cultures, was considered established only when the cultures were positive on more than one occasion for the

same organism. By these criteria, bacteremia was adjudged present in 67 per cent of the dogs with aorticocaval fistulas (Fig. 1), despite penicillin prophylaxis. Staphylococcal and coliform organisms accounted for 37 per cent each and streptococcal organisms for the remaining 26 per cent of the positive blood cultures.

DISCUSSION

In general, these results lend support to the widespread practice of using packed red cells when the occasion for transfusion arises in the presence of possibly impaired cardiac reserve and/or chronic congestive heart failure. This rationale is particularly applicable when the existing deficiency is chiefly that due to loss of red cell mass in the elderly patient with borderline cardiac decompensation. This opinion is based primarily on the right atrial pressure change which, according to Gross, is a most sensitive indicator of increasing blood volume as well as impending right heart failure.

The blood volume determinations revealed an increased total blood volume in both groups. The total blood volume increased an average of 585 milliliters in the dogs receiving 500 milliliters of packed red cells and 779 milliliters in those receiving 1,000 milliliters of whole blood. Thus it is again demonstrated that a portion of the infused plasma leaves the blood stream during or shortly after whole blood transfusion, perhaps through the liver sinusoids, for the infusion of 500 milliliters of plasma, contained in the 1,000 milliliters of whole blood, increased the plasma volume of the recipient animals by only slightly more than 300 milliliters.

The consistently positive blood cultures found in 67 per cent of these animals is in accord with the work of Lillihei and associates. The variability of the infecting organisms is at present inexplainable, other than by chance. The cause of death could in no instance be ascribed to endocarditis, per se, however, as had been previously reported by other investigators.

SUMMARY AND CONCLUSIONS

1. Arteriovenous fistulas 1 centimeter in length were created between the abdominal aorta and the inferior vena cava midway between the renal vessels and the aortic bifurcation in 35 dogs, 20 of which reached the chronic phase of cardiac decompensation.

2. Once chronic cardiac decompensation had developed, the hemodynamic effects of a transfusion of 1,000 milliliters of whole blood and of 500 milliliters of packed red cells were compared by various criteria.

3. The right atrial pressure recording is considered to be a most sensitive gauge of impending "overloading of the circulation," and by this and other criteria a volume of 500 milliliters of packed red cells was shown to produce less of a physiologic insult than an equivalent amount, 1,000 milliliters, of whole blood.

4. It is concluded that, in the presence of serious impairment of the cardiac reserve, the replacement of red cell mass deficit with an infusion of packed red cells imposes less cardiac strain than would the same volume of red cell replacement using whole blood.

REFERENCES

1. Gibson, J. C., II. The clinical significance of the blood volume. Ann. Int. M., 1941, 14: 2014.
2. Gibson, J. H. Use of separated human red cells. N. England J. M., 1944, 250: 976.
3. Gross, R. E. Shattuck lecture: open-heart surgery for repair of congenital defects, N. England J. M., 1959, 260: 1054.
4. Hardy, J. D. Fluid Therapy. P. 206. Philadelphia: Lea & Febiger, 1954.
5. Lillihei, C. W., Bobb, J. R. R., and Visscher, M. B. The occurrence of endocarditis with valvular deformities in dogs with arteriovenous fistulas. Ann. Surg., 1950, 132: 577.

RECONSTRUCTIVE PROBLEMS IN CANINE LIVER HOMOTRANSPLANTATION WITH SPECIAL REFERENCE TO THE POSTOPERATIVE ROLE OF HEPATIC VENOUS FLOW

T. E. STARZL, M.D., Ph.D., HARRY A. KAUPP, JR., M.D., DONALD R. BROCK, M.D., ROBERT E. LAZARUS, B.A., and ROBERT V. JOHNSON, M.D., Chicago, Illinois

ALTHOUGH considerable experimental data have accumulated concerning many organs, there have been few reports of homotransplantation of the liver. Until 1959, the only work had been done by Welch and his associates (9, 34), who were able to obtain function from liver homografts transplanted into the pelvis. Recently, Moore and his associates presented the first accounts of successful homotransplantation of the canine liver to animals with total hepatectomy (21,22). Maximum survival after operation was 12 days.

The techniques to be described for homotransplantation of the liver have previously been briefly outlined (12, 28). The influence of portal flow upon the homografted liver has been analyzed in detail not only because this factor proved to be an important determinant of success or failure but also because the resultant information may have application in a variety of other experimental situations, including those involving hemorrhagic shock. Maximum survival after liver homotransplantation has been 20½ days.

GENERAL METHODS

Seventy-nine liver transplants were performed, using healthy adult mongrel dogs of 10 to 25 kilograms. In most cases, the weights of the donor and recipient animals were closely matched. Both dogs were anesthetized with 25 to 30 milligrams of sodium pentobarbital per kilogram and, after tracheal intubation, placed on respirators. The arterial pressure of the recipient dog was monitored during and immediately after operation with an arterial catheter connected to an aneroid manometer. Venous pressures were read directly from a water manometer attached to an indwelling catheter. The operation was performed under sterile conditions by two, or occasionally three surgeons. In analysis of results, the first 27 hepatic transplants were excluded from consideration because a variety of methods of liver preparation were used with a resultant inconstant quality of grafts.

PRELIMINARY STEPS IN THE RECIPIENT DOG

The abdomen was opened with an upper midline incision. A segment of aorta, 1½ to 2 centimeters in length, was mobilized just above the inferior mesenteric artery for later anastomosis. Next, the mesentery of the caudate lobe of the liver was incised, and the inferior vena cava encircled with a tape, above the entrance of the adrenal veins. The gastrohepatic ligament to the left of the portal triad was then doubly ligated and divided. Finally, common duct and gastroduodenal artery were doubly ligated and divided as close to the duodenum as possible.

From the Departments of Surgery and Pathology, Northwestern University Medical School, Chicago.
Aided by Grant A-3176 from the U. S. Public Health Service, National Institutes of Health, Bethesda, Maryland.

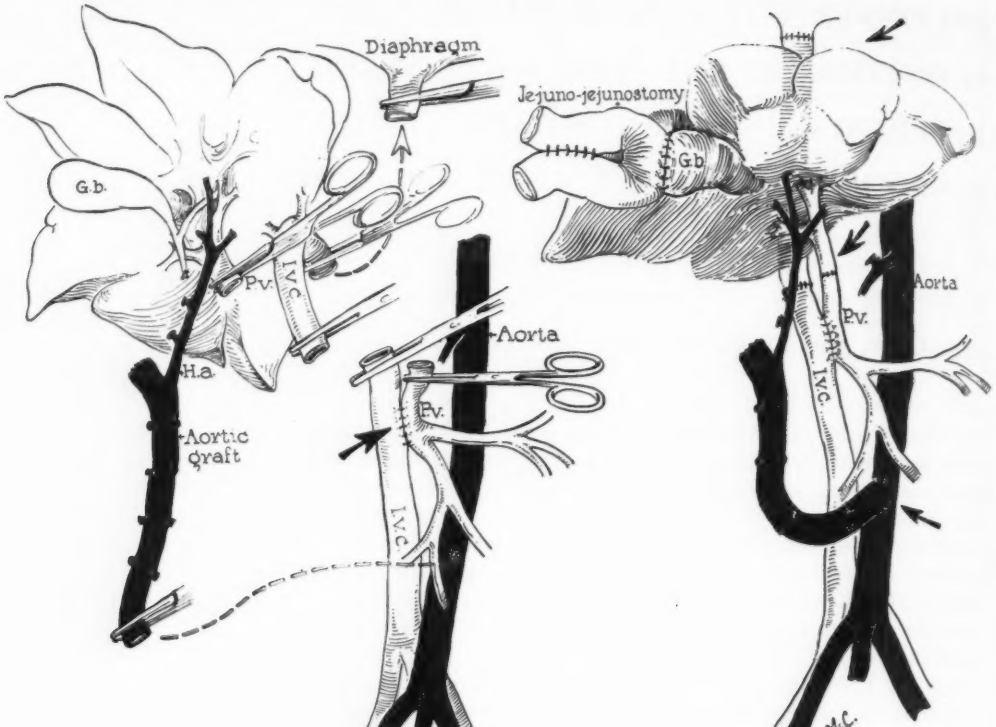


FIG. 1. Basic technique of homotransplantation. a, Donor liver ready for transplant. Note aortic graft removed in continuity with hepatic artery and liver graft. b, Recipient with portacaval shunt and liver removed. c, Donor liver in place.

The portal vein was cleaned off toward the liver until its bifurcation was encountered, taking care to ligate all lymphatics on its surface. When these steps were completed, the only uninterrupted structures remaining in the gastrohepatic ligament were the hepatic artery and the portal vein.

A portacaval shunt was then constructed in as inferior a position as was convenient (Fig. 1b). The exact size and technique of this shunt varied with the different techniques of venous reconstruction during implantation, but in every case the presence of the anastomosis was necessary for decompression of the splanchnic system during implantation of the liver. When the anastomosis was completed, the abdominal wound was closed with towel clips, and attention directed to the donor dog.

PREPARATION OF THE DONOR LIVER

During this operation on the recipient, the donor dog was immersed in an ice bath, and the body temperature reduced to 25 to 30 degrees C. The abdomen of the donor dog was opened through a long midline incision. The abdominal aorta was mobilized proximally to the level of the superior mesenteric artery, ligating and dividing all branches (Fig. 2). The superior mesenteric artery was encircled with a ligature but left intact for the time being.

Next, the stomach and spleen were retracted sharply to the right, and the celiac axis was dissected free from its origin to the trifurcation, where splenic and left gastric arteries were ligated and divided (Fig. 2). Attention was then directed to the portal triad. The gastrohepatic ligament to the left of the triad was first ligated and divided, and the common duct and gastroduodenal artery doubly ligated and divided near the duodenum. The portal vein was freed from its surrounding adventitia in which there were many lymph channels which required ligation. In order to obtain an adequate length of portal vein for subsequent anastomosis, the pancreatic vein was doubly ligated and divided. Several large lymph nodes usually still loosely connected the portal vein and hepatic artery inferiorly, but these were stripped out easily with blunt dissection, leaving the hepatic artery and portal vein skeletonized (Fig. 2). The donor liver was now ready for perfusion in situ.

The previously placed ligature around the superior mesenteric artery was tied. The portal vein was ligated as far inferiorly as possible, and the blunt end of a standard intravenous infusion set directed up the portal vein to the liver. Through this, 1,000 cubic centimeters of cooled (5 to 10 degrees C.) lactated Ringer's solution were used for gravity perfusion of the liver with a pressure head of 60 to 80 centimeters of water (Fig. 2). As soon as perfusion was begun, the animal was bled to death through a catheter inserted into the aorta (Fig. 2). The collected blood was subsequently used for transfusion of the recipient. During the perfusion, the interior of the liver cooled to 10 to 20 degrees C.

The liver was then removed after incision of the diaphragmatic ligaments by transection of the portal vein, the upper abdominal aorta, and the vena cava above and below the liver (Fig. 1a). The open upper end of the aortic graft was ligated. The vena caval cuff above the liver was carefully scrutinized for small holes which, if unrecognized, will lead to air embolus or hemorrhage after the liver is revascularized. A small incision in the gallbladder was made at the site of the proposed cholecystenterostomy to prevent autolysis. The liver was then brought to the table of the recipient animal.

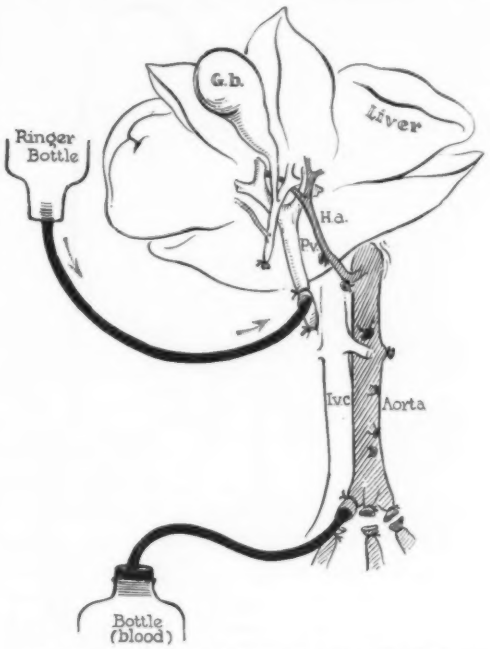


FIG. 2. Preparation of donor liver. Aortic graft prepared. Perfusion of cooled Ringer's solution by gravity through the portal vein and collection of blood from the aorta.

Before evolving this method for preparation of the donor liver, a number of unsatisfactory techniques were employed. These failed generally either because of the use of heparin in the donor with consequent bleeding after transplantation or because the liver was not cooled enough to withstand the effects of ischemia.

HEPATECTOMY IN THE RECIPIENT DOG AND TRANSPLANTATION OF THE DONOR LIVER

After removal of the donor liver, the operating team returned immediately to the recipient dog and inserted an external polyethylene bypass from the femoral to jugular veins (Fig. 3), as described by Kaupp and

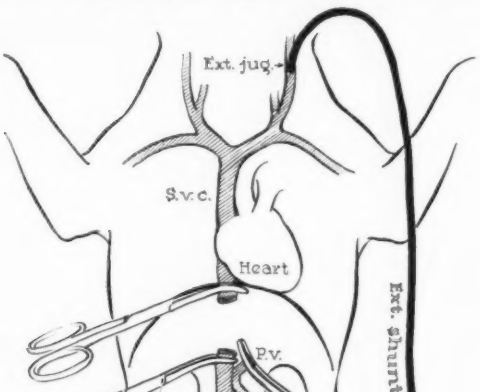


FIG. 3. Decompression of portal and caval venous systems during complete occlusion of vena cava and portal vein by external shunt from femoral vein to external jugular vein.

Starzl (13). After ligation and division of the hepatic artery, the vena cava, above and below the liver, and the portal vein were grasped with Potts' clamps and the liver was removed (Fig. 3). A brisk flow through the external shunt caused decompression of the blocked splanchnic as well as of the caval beds.

The cooled donor liver was positioned in the upper part of the abdomen of the recipient animal (Fig. 1a and b). Anastomosis was performed with continuous No. 5–0 arterial silk between the cuff of recipient vena cava at the diaphragm, which was sharply pulled down to facilitate exposure (Fig. 4), and the short cuff of vena cava on the donor liver. Because of the limited space and short segments of vessels, it was necessary to sew the posterior row from within the vessels (Fig. 4).

Re-establishment of the portal and vena caval return was done in three different ways (Fig. 5). The choice of procedure influenced the type of portacaval shunt previously performed (during preliminary steps in the recipient dog). The first method of venous reconstruction employed the principle of the reverse Eck fistula (Fig. 5a), in which the preliminary portacaval shunt was made at least 1 centimeter in length. After completion of the caval-caval anastomosis above the liver, an end-to-end portal-portal anastomosis was performed, and the open stumps of donor and recipient vena cava below the liver were ligated (Fig. 5a). With release of the clamps, the venous return of both the caval and splanchnic systems were directed through the liver (Fig. 5a).

The second method resulted in anatomic venous reconstruction with the addition of a small portacaval shunt (Fig. 5b). In this case, the preliminary portacaval anastomosis was made small, 4 to 7 millimeters long, without the excision of an ellipse from either vessel. After completing the upper caval-caval anastomosis, the lower caval-to-caval and portal-to-portal anastomoses were performed in anatomic position (Figs. 1c and 5b).

The third method of venous reconstruction resulted in normal venous pathways. The preliminary portacaval anastomosis was 8 to 10 millimeters in length and was used only to decompress the portal system (via the external polyethylene bypass) during the period of acute portal-caval occlusion as the liver was implanted. The portal-portal and lower caval-caval anastomoses were performed anatomically with No. 6–0 and No. 5–0 silk respectively (Fig. 1c). Before the abdomen was closed the portacaval shunt was taken down and the venotomies were closed with No. 6–0 arterial silk (Fig. 5c).

After completing the venous anastomoses, the aortic graft was placed in the right paravertebral gutter and attached with an end-to-side anastomosis to the recipient dog's

aorta, at a variable distance below the renal arteries (Fig. 1c). No. 6–0 arterial silk was used and a button of recipient aorta removed.

Internal biliary drainage was performed with a cholecystojejunostomy, below which was established a jejunojejunostomy (Fig. 1c). Both gastrointestinal anastomoses were performed with a two-layer catgut and silk technique. Splenectomy was carried out, and the abdomen was closed with multiple layers of fine silk.

POSTOPERATIVE CARE

One million units of aqueous penicillin were given on the morning of operation and twice daily during the entire postoperative period. As soon as the operation was completed, a large gastric tube was passed and kept in position until no longer tolerated. Frequent endotracheal aspirations or bronchoscopies were performed until the animal was fully awake.

During operation, 500 cubic centimeters of blood were generally given. During the first 8 to 10 postoperative hours, it was almost always necessary to give another 500 cubic centimeters, even to those dogs in which no bleeding could ever be demonstrated. Intravenous fluids were usually administered for the first 2 or 3 days, after which many dogs tolerated a low protein diet. If the animals stopped eating, intravenous or clysis therapy was reinstituted.

RESULTS

Tolerance of the devascularized liver to ischemia. The time between removal of the cooled donor liver and its revascularization in the recipient dog was 45 minutes, at the least, and in many instances 2 hours. After more than 2 hours, ischemic liver injury occurred which almost always precluded success by any of the described means of reconstruction. When blood flow was restored after ischemia of longer than 2 hours, the liver became tense and dark in color, with histologic evidence of intense congestion. Death followed in a few hours either from

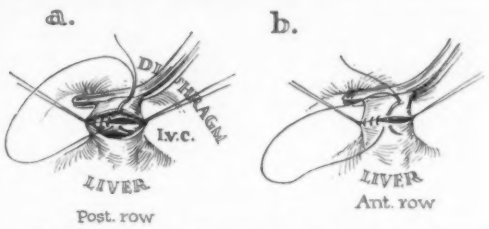


FIG. 4. Technique of caval-caval anastomosis with posterior row being sutured from within.

hemorrhagic gastroenteritis, as a result of hemorrhage from small capsular tears in the distended liver, or from acute hepatic failure.

In preparation of the donor liver, it was important that the liver be cool before any ischemia occurred. For this reason, total body cooling (25 to 30 degrees C.) was carried out in the donor dog before the abdomen was opened. In the event of accidental ischemia during dissection of the portal triad or aortic pedicle, before the liver was further cooled by perfusion, some protection was afforded.

After the liver had been perfused with cold Ringer's solution, its temperature was well maintained at approximately 10 to 16 degrees C. after removal. Shown in Figure 6 is a typical warming curve of the interior of a donor liver, in which the temperature rise was less than 2 degrees C. in 1½ hours.

The value of the external bypass during liver transplantation. In performing the first 20 liver transplants, an external bypass was not used during the period of portacaval

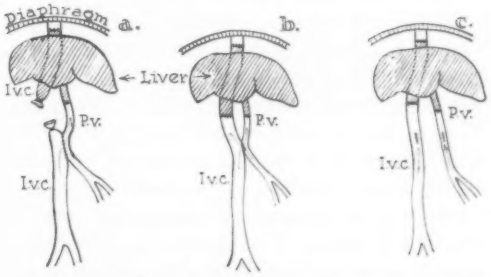


FIG. 5. Methods of venous reconstruction. a, Reverse Eck fistula. b, Anatomic reconstruction with small portacaval shunt. c, Complete anatomic reconstruction with closure of preliminary portacaval shunt.

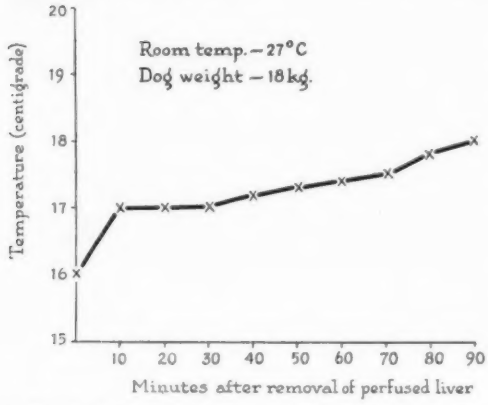


FIG. 6. Rewarming curve of interior of donor liver exposed to room temperature for 1½ hours.

occlusion, since in previous work it had been determined that short term occlusion in the presence of a portacaval shunt was well tolerated (29). Survivals of as long as 6 days were obtained with this technique, but in subsequent experiments the external bypass was routinely used for several reasons. The portacaval occlusion was often for as long as 2 hours, during the latter part of which profound hypotension usually developed. At autopsy, many of the dogs had cardiac lesions similar to the infarcts described by Tanturi after temporary portal occlusion. Finally, hemorrhagic gastroenteritis proved to be a common postoperative complication, and it was not possible to know if this was due to the acute portal hypertension during implantation or to splanchnic venous stasis which developed postoperatively.

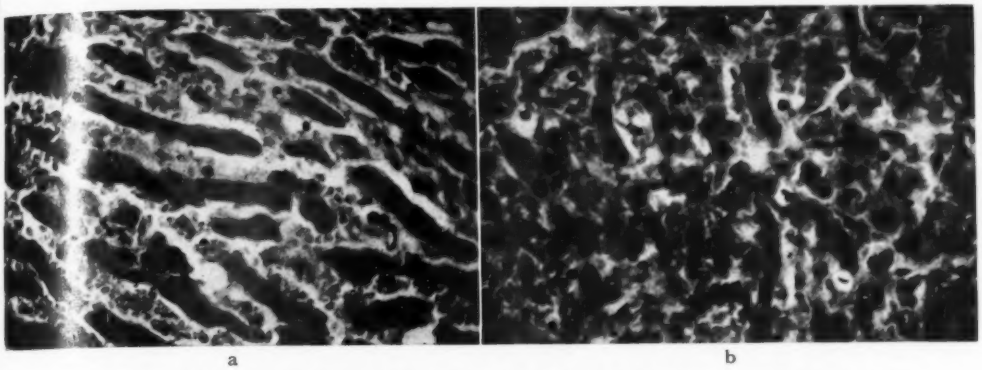
With the external bypass, severe hypotension did not develop. Some fall in blood pressure occurred, but the mean pressure almost always remained above 100 millimeters of mercury. The bowel remained pink. Clotting of the siliconized tube did not generally occur during the bypass.

Acute effect of venous reconstruction with the reverse Eck fistula. Twenty-six hepatic transplants were performed by the method of the reverse Eck fistula (Fig. 5a). Only 4 of the 26 dogs survived for more than 4 days. The other 22 animals died at varying times up to 4 days, in 11 experiments as a result of the inability of the transplanted liver to transmit the required venous flow, with consequent hemorrhagic gastroenteritis. The other early deaths were caused by hemorrhage in 3 dogs, portal thrombosis in 3 dogs, atelectasis in 2 dogs, air embolus in 1 dog, and unknown etiology in 2 dogs.

Most of the unsuccessful experiments followed a highly characteristic pattern. After revascularization, it became obvious that sequestration of blood was occurring in the liver which became swollen, tense, and extremely dark in color. Shortly after, large amounts of lymphatic fluid escaped from the surface of the liver capsule. The portal vein and inferior vena cava distended with pressures as high as 250 millimeters of saline. Superficial lacerations in the transplanted liver began to hemorrhage, and frequently the previously dry portal-portal or portacaval anastomosis began to ooze, sometimes uncontrollably. Within a few minutes, the bowel and stomach lost their normal pink color and assumed a faintly cyanotic hue. Within a few hours, large quantities of fluid accumulated in the gut—at first clear and later blood-stained.

In such cases, a progressively increasing rate of blood transfusion was necessary to maintain the blood pressure. Bloody diarrhea developed, and the animals died in 5 to 15 hours, despite aggressive therapy. Histologic sections of the liver showed acute congestion and early disruption of hepatic cord architecture (Fig. 7a). Sections of the large and small intestine revealed marked congestion and interstitial edema of the entire wall (Fig. 8a and b).

In other experiments, the animals survived the immediate postoperative period, only to die 1 to 4 days postoperatively, usually from gastrointestinal hemorrhage. In these animals, there was histologic evidence of persistent hepatic congestion with distention and coalescence of sinusoids (Fig. 7b). Hepatic cell loss was apparent, especially in central areas. Associated slough of intestinal mucosa and inflammatory in-



a b

FIG. 7. Histologic changes in hepatic outflow block. a, Liver after 10 hours, showing congestion and early loss of architecture with dilated sinusoids. b, Another liver at 36 hours showing persistent congestion and marked disorganization of hepatic architecture. ×214.

filtration of intestinal villi occurred (Fig. 8c).

Four of the 26 liver transplants revascularized with the reverse Eck fistula survived longer than 4 days, or long enough for homograft rejection to be expected to occur. Maximum survival was 9 days.

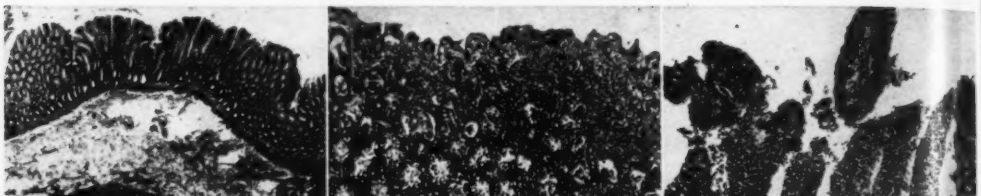
Numerous complications characterized this group of animals. Formation of ascites was excessive, and dissection of the fluid through the incision with wound breakdown occurred in all long term survivals. Pneumonitis and thrombosis of the vascular anastomosis were also late causes of death. Only 1 of the long term survivors was able to eat.

Acute effect of anatomic venous reconstruction with addition of a portacaval shunt. Fifteen transplants were performed by means of anatomic reconstruction of the venous system with the addition of a small portacaval shunt (Fig. 5b). The portacaval anastomosis was deliberately constructed small—4 to 7 millimeters—so that a definitely elevated portal pressure would be necessary in order for large flows to cross the shunt. In this way, it was hoped to decompress the liver and splanchnic circulation in the event of high portal pressures, without unnecessarily diverting portal blood from the liver. Fifteen livers were transplanted in this manner and 6 animals survived for more than 4 days. Nine dogs died in the early postoperative period: 2 of hemorrhage, 4 of atelectasis, 2 of hemorrhagic gastroenteritis, 1 as a result of portal thrombosis. An important contributory cause of death in many of these dogs was a distinctive syndrome consisting of intractable vomiting and retching which began immediately after operation and continued until the death of the dog. This was thought, but not proved, to be due to acute liver failure.

With this technique, the acute congestion of the liver and bowel described for the reverse Eck fistula was seen in only 2 experiments. Generally, the liver became soft and light in color after revascularization, and the bowel remained pink except in those cases in which the shunt was inadvertently made too small to be functional.

Despite the obvious disadvantage of reducing the blood flow to the liver, this technique of reconstruction proved to be the most versatile in one respect. It was possible to perform transplantation without closely matching the size of the donor and recipient animals. Donors were used which weighed as much as 8 to 10 kilograms less than the recipient animals, a disparity in size which precluded success in the other two methods because of the development of splanchnic and hepatic congestion.

Six of the 15 dogs with this type of venous reconstruction lived for more than 4 days.



a b c

FIG. 8. Intestinal changes resulting from outflow hepatic block in dogs with reverse Eck fistula. a, Small intestine after 10 hours showing mucosal and submucosal congestion and submucosal edema. Note intact epithelium. ×11. b, Small intestine in another dog after 18 hours. There is congestion and loss of epithelium of distal portions of villi. ×44. c, Small intestine in a dog dying after 36 hours. Base of villi have partially intact epithelium, but distal villi are edematous and congested with marked slough of epithelial covering. ×44.

Only 2 animals were able to eat consistently. Maximum survival was 9 days. Although it is thought that homograft rejection occurred, a variety of other complications were found at autopsy which could have been independent causes of death.

Acute effect of anatomic venous reconstruction. Eleven dogs had reconstitution of the liver in an anatomic manner, and 8 survived for more than 4 days. The causes of early death were hemorrhagic gastroenteritis in 2 cases, and atelectasis in the third. When this technique was used, the acute bowel congestion described with reverse Eck fistula reconstruction was seldom encountered provided the weights of the donor and recipient dogs were closely matched. However, efforts to use significantly smaller donor than recipient animals resulted in acute bowel congestion and early death.

The clinical behavior of this group of dogs was the most satisfactory of all techniques tried. All 8 long term dogs resumed oral intake promptly, usually after 2 days, and continued to eat until shortly before death, which was presumably due to liver rejection. The average long term survival exceeded that obtained with either of the other methods, as did maximum survival which was 20½ days.

DISCUSSION

The unusual susceptibility of the liver to anoxia has undoubtedly deterred progress in hepatic transplantaion. Welch and associates (9), who transplanted the whole organ to the pelvis of recipient dogs, pointed out that the transferred tissue could not survive if devascularized for more than 30 minutes under normothermic conditions. Disclosures of the protective effect of hypothermia on the ischemic liver by Raffuci, Bernhard, and Huggins and their associates have made transplantation studies more practical.

Despite the protection of hypothermia, undue prolongation of ischemia results in a characteristic liver injury in which the revascularized organ entraps large quantities of blood. The inability of blood to escape is probably due to constriction of small intraparenchymal hepatic veins as shown by Deysach and Thomas and Essex. These vessels have been demonstrated by Arey to have extraordinarily well developed muscular coats in the dog. Similar hepatic con-

gestion, aptly termed "blue liver syndrome" or "outflow block," has been described in the dog in a variety of physiologic circumstances including: anaphylaxis and peptone shock by Mautner and Pick, Simonds, and Weil; temporary devascularization of the liver by Hines and Roncoroni and State and Lichtenstein; histamine injection by Mautner and Pick and Bauer and his associates; perfusion of the isolated liver by Mukravarti and Tripod, Maegaith, and Kestens and his associates; endotoxin shock by MacLean and Weil; and hemorrhagic shock by Frank (6) and Wiggers and their associates.

With transplantation of the liver, the degree of ischemic injury is only one of the influences which contribute to the grave complication of outflow block. The most important secondary factor is the volume of venous blood which is transported to the liver. In the normal dog, it has been shown by Meyer and others that both the splanchnic and inferior caval venous return can be directed through the liver without harmful effects. But the anoxic transplanted liver apparently reacts to such augmented venous flow with outflow block. In contrast, the blue liver developed infrequently when venous inflow was normal or when a decompressing portacaval anastomosis was retained as a permanent feature of the reconstruction. The importance of regulating portal vein inflow in avoiding outflow block during isolated liver perfusion has also been commented upon by McDermott and associates (14), as well as numerous earlier workers.

Another factor contributing to the susceptibility to outflow block of the transplanted or the isolated perfused liver may be the state of denervation in both instances. The confusing literature on vasomotor control of the liver has been summarized by Child. The dominant autonomic influence appears to be sympathetic, with reduction of the size of the liver and increased outflow upon stimulation. Parasympathetic stimulation has resulted in less clear findings. Similarly, epinephrine solutions cause shrinkage of the liver with increased hepatic vein outflow, as shown by Bauer and his associates and by Maegaith, while acetylcholine has a less pronounced but reverse effect. From this information, it would seem quite possible that the denervated liver undergoes vasomotor alterations which promote stasis. Such a mechanism, in addition to contributing to outflow block, could explain the necessity for the large transfusions which are necessary postoperatively, even in the dogs which survive for long term study.

The sequence of events in the bowel following outflow block in the transplanted liver is of interest because of the resemblance of the pathologic changes to those seen in irreversible hemorrhagic shock. For many years, the liver has been suspected of playing an important role in the development of irreversibility. Numerous observers, including Selkurt (25), Wiggers, and Friedman and their associates, have reported increased hepatic vascular resistance after experimental hemorrhage, and it has been reasonable to believe that consequent splanchnic pooling and reduction of circulating blood volume would result. This concept was apparently strengthened by the demonstration of Fine and his associates (7) that viviperfusion of the liver during hemorrhage prevented the hemorrhagic gastroenteritis of irreversible shock. However, Fine's group (6) also demonstrated that decompression of the portal system with portacaval shunt to prevent impounding of blood in the splanchnic system did not prevent the intestinal lesions. Subsequently, attention has been focused on other than hepatic factors in irreversibility, and recently the intestine itself has been suggested as an important primary target organ in shock by Schweinburg and his associates, Selkurt, and Lillehei.

The assessment of the relative importance of the liver and that of bowel in determining irreversibility of shock is still not settled, although there is evidence that both play an important role. In the present study, an experimental situation was present in which

only the liver was subjected to anoxia. The blood pressure generally was never below 100 before, during, or immediately after liver was revascularized. Yet, in the dogs developing outflow hepatic block, shock soon ensued which ultimately was intractable to further transfusion and which eventuated in fatal hemorrhagic gastroenteritis. In this situation, the damage inflicted upon the liver by the transplantation would seem to be solely responsible for the inception and development of irreversible shock.

SUMMARY

The homologous canine liver has been transplanted to recipient animals in which total hepatectomy and splenectomy have been performed. The longest survival after placement of the liver homograft was 20½ days.

Protection from hepatic ischemia for as long as 2 hours was obtained by cooling the donor liver to 10 to 20 degrees C. The arterial supply was restored through a hepatic artery-aortic pedicle which was removed in continuity with the liver and anastomosed to the descending aorta of the recipient. Internal biliary drainage was established.

The volume of venous flow transmitted to the transplanted liver has been shown to be an important determinant of success. When this was excessive, as when both the portal and inferior caval flows were directed through the liver, hepatic outflow block usually developed with consequent fatal congestion of the hepatic and splanchnic beds. When the portal flow was normal or reduced, outflow block rarely occurred.

An attempt has been made to relate the development of outflow block as it occurred in the transplanted liver to other circumstances, including hemorrhagic shock, in which similar phenomena have been observed.

REFERENCES

1. Arey, L. B. Throttling veins in the livers of certain mammals. Anat. Rec., 1941, 81: 21.
2. Bauer, W., Dale, H. H., Poulsson, L. T., and Richards, D. W. The control of circulation through the liver. J. Physiol., Lond., 1932, 74: 343.
3. Bernhard, W. F., McMurrey, J. D., and Curtis, G. W. Feasibility of partial hepatic resection under hypothermia. N. England J. M., 1955, 253: 159.
4. Child, C. G. The Hepatic Circulation and Portal Hypertension. Pp. 90-106. Philadelphia: W. B. Saunders Co., 1954.
5. Deysach, L. J. The nature and location of the "sphincter mechanism" in the liver as determined by drug actions and vascular injections. Am. J. Physiol., 1941, 132: 713.
6. Frank, H. A., Glotzen, P., Jacob, S. W., and Fine, J. Traumatic shock—XIX, hemorrhagic shock in Eck fistula dogs. Am. J. Physiol., 1951, 167: 508.
7. Frank, H. A., Seligman, A. M., and Fine, J. Traumatic shock—XIII, the prevention of irreversibility in hemorrhagic shock by viviperfusion of the liver. J. Clin. Invest., 1946, 25: 22.
8. Friedman, E. W., Frank, H. A., and Fine, J. Portal circulation in experimental hemorrhagic shock; in vivo roentgen ray studies. Ann. Surg., 1951, 134: 70.
9. Goodrich, E. O., Welch, H. F., Nelson, J. A., Beecher, T. S., and Welch, C. S. Homotransplantation of the canine liver. Surgery, 1956, 39: 244.
10. Hines, J. R., and Roncoroni, M. Acute hepatic ischemia in dogs. Surg. Gyn. Obst., 1956, 102: 689.
11. Huggins, C., Carter, E., and McDermott, W. Differential hypothermia in experimental hepatic surgery. Arch. Surg., 1957, 74: 327.
12. Kaupp, H. A., Lazarus, R. E., and Starzl, T. E. Complete homotransplantation of the liver after total hepatectomy in dogs. (Abstract) Presented at the American Association for Study of Liver Disease. Chicago, Nov. 5, 1959. Gastroenterology, 1960, 38: 794.
13. Kaupp, H. A., and Starzl, T. E. The use of an external by-pass during experimental total hepatectomy. Surgery, in press.
14. Kestens, P. J., Austen, W. G., and McDermott, W. V., Jr. Biochemical and physiologic studies on the viable extracorporeal liver. Surgical Forum; Clinical Congress 1959. Vol. X, p. 225. Chicago: American College of Surgeons, 1960.
15. Lillehei, R. C. The intestinal factor in irreversible hemorrhagic shock. Surgery, 1957, 42: 1043.
16. MacLean, L. D., and Weil, M. H. Hypotension (shock) in dogs produced by Escherichia coli endotoxin. Circ. Res., 1956, 4: 546.
17. Maegaith, B. G. Microanatomy of the hepatic vascular system. Trans. Tenth Conf., May 21-22, 1951. Josiah Macy Jr. Foundation, 1951, pp. 181-204.
18. Makravarti, M., and Tripod, J. The action in the perfused liver of acetylcholine, sympatheticomimetic substances and local anesthetics. J. Physiol., Lond., 1940, 97: 316.
19. Mautner, H., and Pick, E. P. Ueber die durch Schockgifte erzeugten Zirkulationsveränderungen; der Einfluss der Leber auf Blutdruck und Schlagvolumen. Arch. exp. Path., Lpz., 1929, 142: 271.
20. Meyer, W. H., and Starzl, T. E. The reverse porta-caval shunt. Surgery, 1959, 45: 531.
21. Moore, F. D., Smith, L. L., Gruber, U. H., Demissianos, H. V., Burnap, T. K., and Dammin, G. J. One stage homotransplantation of the canine liver after total hepatectomy. Presented at the American College of Surgeons meeting, Atlantic City, Sept. 28, 1959.
22. Moore, F. D., Wheeler, H. B., Demissianos, H. V., Smith, L. L., Belankura, O., Abel, K., Greenberg, J. B., and Dammin, G. J. Experimental whole organ transplantation of the liver and of the spleen. Ann. Surg., in press.
23. Raffucci, R. L., Lewis, F. J., and Wangensteen, O. H. Hypothermia in experimental hepatic surgery. Proc. Soc. Exp. Biol., N. Y., 1953, 83: 639.

24. SCHWEINBURG, F. B., SHAPIRO, P. B., FRANK, E. D., and FINE, J. Host resistance in hemorrhagic shock—IX, demonstration of circulating lethal toxin in hemorrhagic shock. Proc. Soc. Exp. Biol., 1957, 95: 646.
25. SELKURT, E. E. Effect of acute hepatic ischemia on splanchnic hemodynamics and on BSP removal by liver. Proc. Soc. Exp. Biol., N. Y., 1954, 87: 307.
26. Idem. Mesenteric hemodynamics during hemorrhagic shock in the dog with functional absence of the liver. Am. J. Physiol., 1958, 193: 599.
27. SIMONDS, J. P. Fundamental physiologic reactions in anaphylactic and peptone shock. J. Am. M. Ass., 1919, 73: 1437.
28. STARZL, T. E. Discussion of (22). Ann. Surg., in press.
29. STARZL, T. E., BERNHARD, V. M., BENVENUTO, R., and CORTES, N. A new method for one stage hepatectomy in dogs. Surgery, 1959, 46: 880.
30. STATE, D., and LICHTENSTEIN, I. A study of the genesis of shock associated with experimentally induced hepatic necrosis in dogs. Surgery, 1956, 39: 12.
31. TANTURI, C., MEJIA, R. H., CANEPA, J. F., and GOMEZ, O. T. Electrocardiographic and humoral changes in transient occlusion of the portal vein in the dog. Surg. Gyn. Obst., 1960, 110: 537.
32. THOMAS, W. D., and ESSEX, H. E. Observations on the hepatic venous circulation with special reference to the sphincteric mechanism. Am. J. Physiol., 1949, 158: 302.
33. WEIL, W. R. Studies in anaphylaxis—XXI, anaphylaxis in dogs; a study of the liver in shock and peptone poisoning. J. Immun. Balt., 1917, 2: 525.
34. WELCH, C. S. A note on the transplantation of the whole liver in dogs. Transplant. Bull., 1955, 2: 54.
35. WIGGERS, C. J., OPDYKE, D. F., and JOHNSON, J. R. Portal pressure gradients under experimental conditions including hemorrhagic shock. Am. J. Physiol., 1947, 146: 192.

INTERMITTENT COLD CORONARY PERFUSION AS AN ADJUNCT TO OPEN HEART SURGERY

WILLIAM F. BERNHARD, M.D., HANS F. SCHWARZ, M.D., and
NETAR P. MALLICK, B.Sc., M.B., Ch.B., Boston, Massachusetts

ELECTIVE ARREST of cardiac muscular activity during cardiopulmonary bypass can be produced by selective cooling of the myocardium. This is accomplished by perfusion of the coronary arteries with cold, oxygenated blood at predetermined flow rates of 30 to 150 cubic centimeters per minute. A rapid reduction in myocardial temperature occurs, resulting in hypothermic arrest of the heart at a mean temperature of 14 degrees C. Interruption of coronary perfusion is then possible for multiple periods of 15 to 25 minutes, providing a dry, quiet operative field.

Spontaneous rewarming of the myocardium takes place during the absence of perfusion due to contact between the heart and the normothermic mediastinal structures. For this reason, intermittent coronary perfusion is obligatory. The observed metabolic requirements of the heart are rapidly satisfied by the flow of oxygenated blood, and this permits subsequent interruption of coronary circulation.

This study is presented to evaluate the effects of prolonged, hypothermic, cardiac arrest in the normothermic dog, and to describe a stainless steel heat exchanger designed for use in these experiments.

EXPERIMENTAL METHODS AND MATERIALS

Eighteen adult mongrel dogs of either sex, weighing 11 to 17 kilograms, were used. All animals were anesthetized with the intravenous administration of 30 milligrams of pentobarbital sodium per kilogram of weight and were intubated. Respirations were controlled with a Bennett automatic respirator which delivered a peak positive pressure of 25 centimeters of water. Polyethylene cannulas were inserted into the left femoral artery and aortic arch (proximal to a Satinsky clamp) to permit determination of mean arterial blood pressure and coronary perfusion pressure during cardiac cooling. All pressures were measured with a Statham pressure transducer and recorded with a Sanborn direct writer. A cannula was also passed into the inferior vena cava through the left femoral vein to record central venous pressure. Serial electrocardiograms were obtained in each animal (standard lead II) and recorded with a Sanborn visocardiette.

Myocardial temperatures were measured with a thermocouple mounted on the tip of a 22 gauge needle. Individual thermistors connected to a multiple channel telethermometer recorded temperatures in the oxygenator, cardiac cooling unit, and the rectum of the dog.

A bilateral thoracotomy was performed in all animals, entering the fifth intercostal space on each side. Cannulation of the cavae was carried out after the intravenous administration of 1.0 milligram of heparin per kilogram of body weight. At the time of decannulation an antiheparin compound, hexadimethrine bromide, was given in a 1 to 1 ratio.

Cardiopulmonary bypass was established with a Gross model siphon-filling, disc oxygenator and two DeBakey pumps. Flow rates were maintained between 70 and 100

From the Laboratory for Surgical Research, The Children's Hospital, and the Department of Surgery, Harvard Medical School, Boston.

These studies were supported by research grants from the National Heart Institute, National Institutes of Health, U. S. Public Health Service, and the American Heart Association.

cubic centimeters per kilogram of body weight per minute. Cannulation of the left auricle and ventricle, as well as of the right side of the heart, was necessary to include the return of bronchial collateral flow and coronary sinus blood to the oxygenator. Arterial inflow to the animal from the machine was accomplished through a metal cannula inserted into the right femoral artery. A small volume of blood from this line was shunted into a graduated reservoir connected to the cooling unit and was delivered to the coronary ostia at flows of 30 to 150 cubic centimeters per minute. Perfusion was accomplished by means of a precalibrated Sigma motor pump, and the flow was checked frequently by observing the rate of fall of blood in the reservoir during a 60 second interval.

Two different cooling units were utilized in these experiments. One consisted of tygon tubing coiled in an ice bath, and the other was a stainless steel heat exchanger with a capacity of 300 cubic centimeters (Fig. 1). The components of the latter unit consisted of a tube assembly (80 straight tubes, 30.5 centimeters in length and 0.5 centimeter in diameter), 2 end-plates, a pyrex reservoir graduated in cubic centimeters, and a 35 liter ice bath. All parts assembled and disassembled with ease to facilitate cleaning and sterilization.

The body temperature of each animal was maintained between 33 and 36 degrees C. during the period of extracorporeal circulation. This was accomplished by means of a hot water heating element connected to the oxygenator, and an electric blanket positioned under the thorax of the dog.

Perfusion of the coronary arteries was carried out with oxygenated blood reduced to a temperature of from 3 to 8 degrees C. (Fig. 2). At the onset of myocardial cooling, the heart was insulated from the normothermic mediastinal structures with a rubber sheet to minimize spontaneous rewarming. Intermittent periods of perfusion at high flow rates—100–150 cubic centimeters per minute—or prolonged perfusion at a low

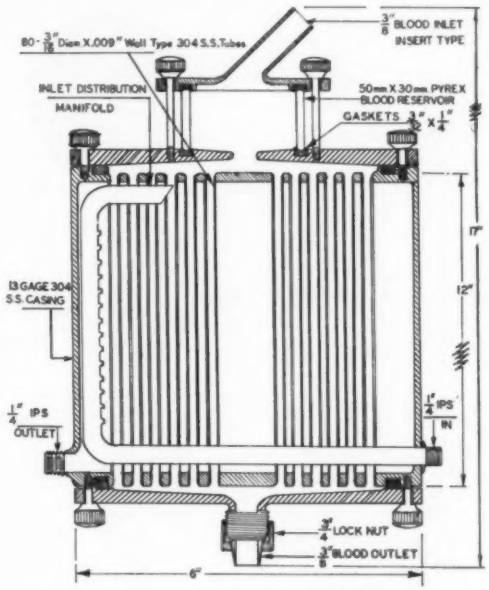


FIG. 1. The components of a stainless steel heat exchanger designed for the production of selective cardiac hypothermia.

rate of flow—30 cubic centimeters per minute—was sufficient to maintain myocardial temperatures in the range of 5 to 20 degrees C. Interruptions of coronary circulation were produced in all animals for multiple periods of 15 to 25 minutes. Upon completion of the interval of cardiac arrest the perfusion catheter and rubber insulation were removed, and rewarming was accomplished by release of the aortic cross-clamp.

In some dogs, coronary blood flow determinations were made by the Kety-Schmidt nitrous oxide method (3). A standard sampling period of 10 minutes was sufficient to allow satisfactory equilibration of the nitrous oxide between arterial blood and myocardium. Blood samples were obtained through polyethylene catheters positioned in the coronary sinus and oxygenator. All specimens were drawn in heparinized syringes, sealed with mercury and refrigerated until gas determinations could be carried out. The nitrous oxide determinations were made with a Van Slyke apparatus (5), and

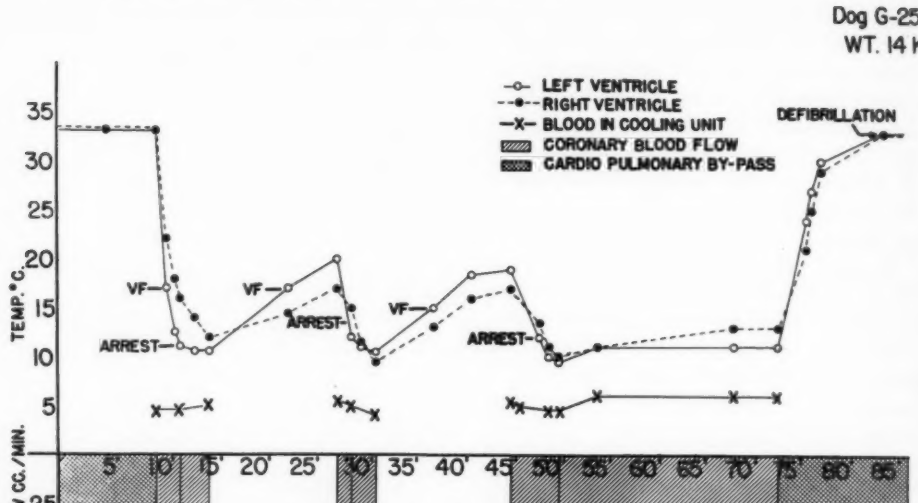


FIG. 2. Chart of rapid myocardial cooling in a single animal of this study. Gradual spontaneous rewarming of the heart occurred during interruption of coronary perfusion. Reperfusion with cold, oxygenated blood rapidly reduced the myocardial temperature and produced hypothermic cardiac arrest.

the oxygen capacity and percentage saturation were measured by utilizing the spectrophotometric method described by Stainby and associates.

RESULTS

Efficiency of myocardial cooling and rewarming. Coronary perfusion with cold, oxygenated blood resulted in ventricular fibrillation at a mean temperature of 18.0 degrees C. and cardiac arrest at a mean temperature of 12.3 degrees C. The average time interval occupied by cooling was 4.7 minutes, while rewarming occurred over a slightly longer period, 6.0 minutes. Electrical defibrillation of the heart was accomplished without difficulty when the myocardial temperature was in the range of 29.0 degrees to 32.0 degrees C. (Fig. 3). After resuscitation, the mean arterial pressure and the central venous pressure of each dog remained in the normal range, and a period of partial bypass to support circulation was unnecessary. Electrocardiograms obtained prior to cooling and after defibrillation showed no essential change in configuration. During cold perfusion, the Q-T interval progressively lengthened and was associated with bradycardia, and an increase in the amplitude of the T wave (Fig. 3).

Cardiac arrest was maintained by intermittent perfusion for periods of 43 to 83 minutes. Longer intervals of arrest were not attempted because the total duration of cardiopulmonary bypass was arbitrarily limited to 120 minutes.

Survival data. Four animals in the series expired within the first 48 hours postoperatively, and postmortem examination disclosed a large hemothorax in each instance.

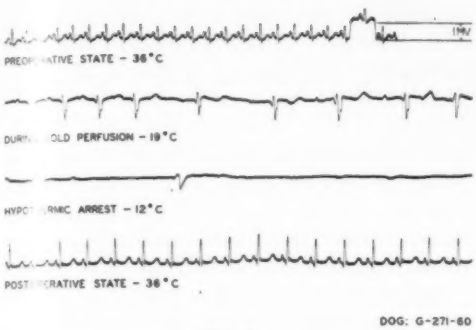


FIG. 3.

FIG. 3. A reproduction of serial electrocardiographic tracings recorded from a representative experimental animal showing changes during cold coronary perfusion.

FIG. 4. A graphic presentation of myocardial oxygen utilization in the normothermic and hypothermic heart.

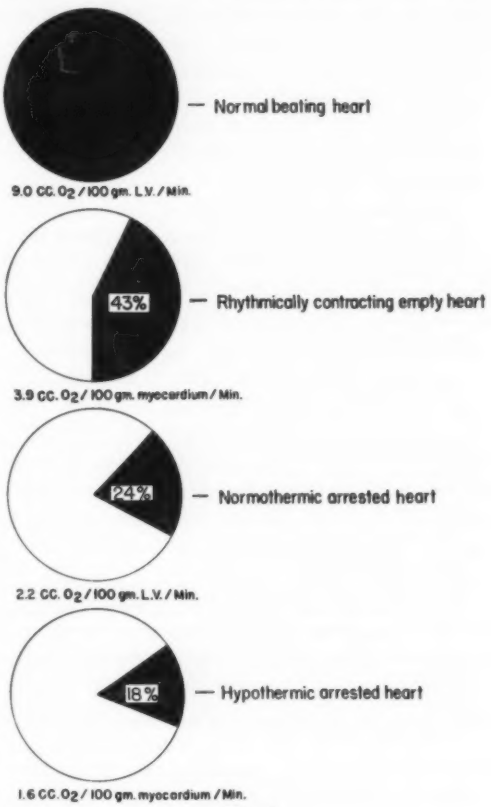

Normal beating heart
9.0 CC. O2 / 100 gm. L.V. / Min.
43%
Rhythmically contracting empty heart
3.9 CC. O2 / 100 gm. myocardium / Min.
24%
Normothermic arrested heart
2.2 CC. O2 / 100 gm. L.V. / Min.
18%
Hypothermic arrested heart
1.6 CC. O2 / 100 gm. myocardium / Min.

Fig. 4.

No other abnormalities were noted. Fourteen other dogs who lived from 3 to 60 days were considered as survivors.

Coronary blood flow and perfusion pressure relationships. Perfusion pressures and coronary blood flow data from 2 representative animals were recorded. Hypothermic cardiac arrest was achieved in each animal with a pump perfusion rate of 100 cubic centimeters per minute. This high flow resulted in mean perfusion pressures of 125 and 138 millimeters of mercury respectively. These pressures were only slightly increased over the pressures observed in the same animals in the normothermic state.

Myocardial metabolism. In some animals, a determination of myocardial oxygen consumption was made during ventricular fibrillation in the temperature range of 10 to 17 degrees C. When compared with the oxygen consumption of the heart in hypothermic arrest—8.5 to 15 degrees C.—no significant difference was found.

DISCUSSION

Elective cardiac arrest during cardiopulmonary bypass greatly facilitates the correction of certain valvular and intracardiac defects. Current methods employ potassium citrate or hypoxic arrest and are often associated with grave difficulties in cardiac resuscitation. Selective myocardial cooling produced by cold coronary perfusion is presented as an effective, safe alternative. A dry, quiet operative field can be obtained by utilizing intermittent perfusion with multiple interruptions of flow for intervals of 15 to 25 minutes. After cardiac rewarming, conversion from ventricular fibrillation to a sinus rhythm is accomplished without difficulty.

In the cold heart, high rates of coronary perfusion are possible without a significant increase in perfusion pressure. The original observation was made by Berne during isolated perfusion of the left common coronary artery with blood at a temperature of 20 degrees C. Allowing for a time lag of 1 to 2 minutes, an inverse relationship was noted

between the temperature of the perfusate and the rate of coronary flow. The current experiments confirm these data in a lower temperature range (8.5 to 20 degrees C.) and they indicate the occurrence of a very marked decrease in coronary vascular resistance.

High flow, cold perfusion of the coronary arteries also satisfies the existing myocardial oxygen and substrate requirements. In hypothermic arrest (8.5 to 15 degrees C.), the oxygen utilization of the heart amounts to 1.6 cubic centimeters per 100 grams whole heart per minute. This is a relatively high consumption when compared to the requirements of the normothermic arrested heart—2.2 cubic centimeters per 100 grams left ventricle per minute—and of the normothermic beating heart—9.0 cubic centimeters per 100 grams left ventricle per minute (Fig. 4).

When coronary perfusion is interrupted fibrillatory contractions of the myocardium reappear. This is a result of spontaneous rewarming of the heart which occurs at an approximate rate of 0.5 degree C. per minute. However, in the temperature range of 10 to 17 degrees C., the myocardial oxygen utilization of the fibrillating heart is not significantly greater than in the cold, arrested heart. Therefore, reperfusion can be safely delayed in the presence of ventricular fibrillation at least until a temperature of 17 degrees C. is attained.

SUMMARY

1. Selective cardiac hypothermia produced by cold coronary perfusion with oxygenated blood is presented as a method for prolonged, safe cardiac arrest.

2. Intermittent perfusion is a necessity because of spontaneous myocardial rewarming. This occurs primarily because of contact between the heart and the normothermic mediastinal structures.

3. As a result of a decrease in coronary vascular resistance, high coronary perfusion flows are possible in the cold heart without significantly increasing perfusion pressure.

4. An evaluation of the metabolic requirements of the cold, fibrillating heart and the heart in hypothermic arrest indicates no significant difference in oxygen utilization.

5. A stainless steel heat exchanger used in these experiments is described in detail.

REFERENCES

1. Berne, R. M. Coronary blood flow during hypothermia. In: The Physiology of Induced Hypothermia. P. 165. Washington: National Research Council, 1956.
2. Gross, R. E., Sauvage, L. R., Pontius, R. G., and Watkins, E. Experimental and clinical studies of siphon-filling disc oxygenator system for complete cardiopulmonary by-pass. Ann. Surg., 1960, 151: 285.
3. Schmidt, C. F. The Cerebral Circulation in Health and Disease. Springfield: Charles C Thomas, 1950.
4. Stainby, W. W., Fales, J. T., and Lilienthal, J. L., Jr. A rapid spectrophotometric method for determining oxygen content of dog's blood. J. Appl. Physiol., 1955, 7: 577.
5. Van Slyke, D. D., and Neill, J. M. The determination of gases in blood and other solutions by vacuum extraction and manometer measurement. J. Biol. Chem., 1924, 61: 523.

ACUTE NECROTIZING COLITIS PROXIMAL TO OBSTRUCTING NEOPLASMS OF THE COLON

ALFRED HURWITZ, M.D., F.A.C.S., and RENE A. KHAFIF, M.D., Brooklyn, New York

ACUTE NECROTIZING INFLAMMATION proximal to carcinoma of the colon, which is not completely obstructive, is not a widely recognized clinical entity because the bowel is usually not opened and examined at the time of operation and because the surgeon's attention is focused primarily on the carcinoma. The occurrence of this complication was mentioned by MacCallum and by Kasich and his associates. However, they did not report upon any personal cases nor did they include references pertaining to this particular entity. Dennis and Karlson stated that they had personally observed this complication in 4 patients.

Thirteen patients with acute necrotizing colitis proximal to carcinoma of the colon, which had caused incomplete obstruction, have been seen at Maimonides Hospital from 1950 to 1959, and these cases are reported herewith. The following criteria were employed in the selection of the patients included in this study; (1) incomplete obstruction of the large bowel secondary to a neoplasm; (2) colitis of a nonspecific type confined to the colon proximal to the lesion–no past history of colitis, negative sigmoidoscopic findings, no evidence of amebic or idiopathic ulcerative colitis. The pathologic diagnosis in most instances was acute inflammatory necrotizing colitis. In Table I, pertinent data are given regarding these 13 patients. In Cases 1 and 3, rather unusual features were present.

CASE REPORTS

CASE 1. A 61 year old white female entered the hospital because of progressive constipation of 4 months' duration, intermittent cramplike pain, anorexia, vomiting, and a weight loss of 16 pounds. Physical examination showed the abdomen to be slightly distended and tender with marked tympanism and hyperperistalsis. Temperature and pulse were both normal. Roentgenogram of the abdomen showed partial obstruction of the large bowel as well as distension of the large and small bowel. Examination of the stool was positive for occult blood.

At operation, a napkin-ring carcinoma of the sigmoid colon was found with metastases to the regional lymph nodes. A left hemicolectomy with an end-to-end anastomosis was performed, and an appendicostomy was also done. The pathologist's report indicated an annular carcinoma encircling the bowel wall which almost completely occluded the lumen. The bowel proximal to the lesion was extremely edematous and dilated. Near the proximal line of resection, several large, irregular, ulcerated areas were observed. The remaining mucosa proximal to the lesion had a mottled hemorrhagic appearance, and normal rugae were not present (Fig. 1). The mucosa distal to the lesion was normal.

Postoperatively, the patient was well for 5 days, and then developed severe pain in the left upper quadrant of the abdomen. On the following day, dark brown material was vomited, respiration became labored, and hypotension developed. A Cantor tube was passed and oxygen, neosynephrine hydrochloride, blood, and antibiotics were administered. The appendicostomy incision was reopened but no evidence of peritonitis was found. There was a great amount of drainage through the Cantor tube. Three days later a fecal fistula was observed at the site of the incision. Seven days later, on the seventeenth postoperative day, the patient expired. Permission for autopsy was not obtained.

Because of the development of a fecal fistula, it seems likely that the cause of death was peritonitis, secondary to leakage through the anastomosis. The colitis in the bowel proximal to the lesion, which extended to the line of resection, probably deterred healing of the anastomosis from which there had been leakage on the fifth postoperative day. Appendicostomy proved to be an in-

From Department of Surgery, Maimonides Hospital and State University of New York, Downstate Medical Center.

This investigation during Dr. Khafif's Postdoctoral Fellowship No. HF9789 from the National Heart Institute, U. S. P. H. S.

TABLE I.

Case No.	*Clinical features related to colitis*	*Diversionary operation*	*Resection*	*Features of colitis*	*Postoperative course*
1		Appendicostomy, at time of surgery	Anterior resection	Necrotizing ulcerative colitis	Blow out of the suture line, fecal peritonitis, death
2		0	Abdominoperitoneal resection	Necrotizing ulcerative colitis	Uneventful
3	Pain, tenderness, spasm, diarrhea	0	Anterior resection	Lesion between 2 carcinomas	Uneventful
4	Acute condition of abdomen, diarrhea, fever	Transverse colostomy, 25 days before surgery	Anterior resection	Perforations proximal to the carcinoma	Uneventful
5	Temp. 101, pulse 110	Cecostomy, 9 days before surgery	Hartmann operation	Necrotizing ulcerative colitis	Uneventful
6	5 day history of acute enterocolitis	Cecostomy, at surgery	Wedge resection	Necrotizing ulcerative colitis	Uneventful
7	Temp. 103, pulse 140	Cecostomy, 19 days before surgery	Wedge resection	Necrotizing ulcerative colitis	Blow out of the cecostomy, recovery
8	Abdominal tenderness	0	Resection of right half of colon ileotransverse colostomy	Cecal ulcers	Uneventful
9	0	0	Ileoproctostomy	Linear ulcers	Uneventful
10	Resembled acute appendicitis, temp. 102	0	Resection of right half of colon ileotransverse colostomy	Cecitis	Uneventful
11	Diarrhea	Transverse colostomy, at surgery	Anterior resection	Necrotizing ulcerative colitis	Uneventful
12	Left lower quadrant, tenderness	Transverse colostomy, 21 days before surgery	Anterior sigmoid resection	Necrotizing ulcerative colitis	Uneventful
13	Resembled acute diverticulitis	Transverse colostomy, 21 days before surgery	Anterior sigmoid resection	Perforations proximal to the carcinoma	Uneventful

adequate procedure for decompression of the large bowel.

CASE 3. A 50 year old white male entered the hospital because of severe abdominal cramps, nausea, vomiting, and diarrhea of 1 day's duration. A weight loss of 15 pounds was reported as well as progressive weakness during the year before admission. Physical examination revealed slight abdominal distention with hyperactive bowel sounds and minimal tenderness with rebound tenderness in the left lower quadrant of the abdomen. Temperature was 102 degrees and the leucocyte count 26,500, but both subsequently returned to normal. Results of barium enema tests revealed 2 canalizing lesions of the left half of the colon.

At operation, 2 napkin-ring carcinomas were found in the left half of the colon, and there was marked distention between them. A partial colectomy was performed. The pathologic report stated that large areas of ulcerations covered by a hemorrhagic and purulent exudate were found between the 2 lesions (Fig. 2).

The postoperative course was uneventful.

This patient had peritoneal signs in keeping with an intraperitoneal inflammatory process localized to the left lower quadrant. The inflamed mucosa was limited to the bowel between the 2 carcinomas where the distention was most marked. The line of anastomosis was devoid of disease, and the postoperative course was uncomplicated.

DISCUSSION

Acute necrotizing colitis proximal to an obstructing carcinoma of the large bowl consists of large, irregular ulcerations. The mucosa is usually covered by a hemorrhagic and purulent exudate. The islands of mucosa between the ulcerations are edematous and congested. The wall of the diseased colon is usually thickened, stiff and friable. Histologically, areas of necrotic mucosa, the forerunners of the ulcers, are often seen. There is marked acute and subacute inflammation, and microabscesses are

frequently present. The severity of the inflammatory reaction varies from edema and linear ulcerations to necrosis of the bowel with perforation and peritonitis. There does not seem to be any correlation between the severity of the inflammation and the degree of obstruction or distension of the large bowel. In Case 11, for example, there were marked inflammatory changes despite the fact that the stenosis produced by the carcinoma was minimal.

The disease entity described in this article may be secondary to the effects of partial obstruction and/or to the bacterial proliferation caused by stagnation of the fecal material above the stricture. Since complete obstruction did not exist in any of our patients, it is unlikely that diastatic effects of severe pressure played a major role in the etiology of the necrotizing colitis. Moreover, our cases are to be differentiated from those in which the inflammation and perforation are confined to the site of the carcinoma itself. They, also, differ markedly from those of stercoraceous ulcers. The salient features of stercoraceous ulcers, secondary to severe constipation and fecal impactions, are the absence of inflammation and necrosis, and the limitation of the disease to ulcers at the points of pressure made by the fecal masses present.

The dual factors, distension and infection, undoubtedly play the important roles in the pathogenesis of this complication. There have been several reports upon the effects of acute distention of segments of the large bowel produced experimentally in animals and in cadavers, and Nix, Wheeler, and Maddock have reported 2 cases of acute necrotizing inflammation of the colon proximal to a complete intestinal obstruction. Distention, which is the main etiologic factor in colitis secondary to acute obstruction, played a less significant role in the condition of our patients. In fact it was completely absent in Case 11. We believe that the bacterial proliferation due to the stagnation of fecal material is probably the major factor in the causation of acute necrotizing colitis secondary to incomplete obstruction of the large bowel.

FIG. 1. Case 1. The sigmoid colon can be seen in the lower portion of the illustration. There is complete loss of mucosal pattern with marked edema and hemorrhage in the proximal segment. Two large ulcers, 1 of which is at the proximal line of resection, can be visualized.

The diagnosis of necrotizing colitis should be considered if diarrhea, pain, tenderness, spasm, hyperpyrexia, or tachycardia are present. All resected specimens should be opened and examined at the time of operation and cultures taken. If colitis is noted in the segment of bowel proximal to the carcinoma, then the proximal loop should be examined through a sterile sigmoidoscope and resection extended until normal bowel is reached. If extension of the operation seems ill advised because of the condition of

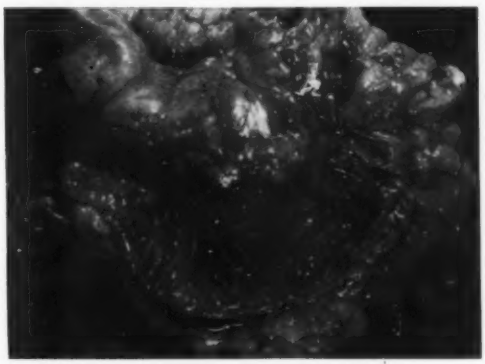


FIG. 2. Case 3. Specimen of excised left half of colon shows the hemorrhagic and ulcerated mucosa in the segment of distended colon between 2 carcinomas.

the patient, or the extent of the colitis, the surgeon may elect to exteriorize both limbs rather than perform an anastomosis, or he may perform an anastomosis with a diverting proximal colostomy to help ensure the integrity of the suture line. Windsberg reported the successful performance of resection of the large bowel with end-to-end anastomosis in 7 cases of complete obstruction. Although this procedure might be safe in selected cases, the anastomosis would be contraindicated if examination of the bowel at operation revealed inflammation proximal to the obstruction. In several instances, we found it folly to anastomose the inflamed proximal bowel without performing a protective diverting colostomy. Severe colitis in the proximal bowel deterred healing of the anastomosis, and in 1 case leakage through the suture line caused peritonitis which was fatal. Cecostomy which was performed in the earlier cases in our series appeared to be less efficacious.

If a colostomy has been performed, the colonic loops should be examined through a sigmoidoscope and a barium enema given before closure of the colostomy is contemplated. If the inflammation is still subsiding, then the surgeon should postpone the operation until the remission is complete. If the inflammation persists after a long period of time, resection with removal of all the diseased bowel and anastomosis of the normal limbs may be the elected procedure.

Lesions in the right half of the colon or in the proximal transverse colon pose less of a problem since colectomy of the right half of the colon with excision of the distal ileum can be performed with the removal of all of the inflamed colon. The ileum is usually intact and its anastomosis to the colon should be safe.

SUMMARY

Thirteen cases of acute necrotizing colitis proximal to carcinomas of the colon producing partial obstruction of varying degrees are reported. The existence of this complication should be suspected if pain, tenderness, spasm, presence of a mass, tachycardia, or hyperpyrexia are present preoperatively.

The degree of inflammation varies from an edematous state to necrotic ulceration and perforation. The resected specimen should always be examined at the time of operation. If colitis is found, then a more extensive resection, exteriorization of the colonic limbs, or anastomosis with a proximal diverting colostomy should be performed. The procedure selected depends upon the extent of the disease and the condition of the patient.

REFERENCES

1. Dennis, C., and Karlson, K. E. Surgical measures as supplement to the management of idiopathic ulcerative colitis. Surgery, 1952, 32: 892.
2. Kasich, A. M., Weingarten, B., and Brown, M. L. Malignant degeneration in ulcerative colitis. Med. Clin. N. America, 1949, p. 1421.
3. MacCallum, W. G. Textbook of Pathology. 7th rev. ed. Pp. 263–264. Philadelphia: W. B. Saunders Co., 1947.
4. Nix, T., Wheeler, J., and Maddock, W. G. Fatal acute necrotizing colitis resulting from intestinal distension. Q. Bull. Northwest. Univ. M. School, 1952, 26: 157–160.
5. Windsberg, E. Intestinal obstruction of the colon due to malignancy; single stage decompression and resection. Surgery, 1959, 46: 305–318.

A ROENTGENOGRAPHIC AND CLINICAL STUDY OF THE LARYNX AND PHARYNX

R. SHEEHAN, M.D., F. LESSMANN, M.D., F. MARCHETTA, M.D., F.A.C.S., and R. K. LIN, M.D., Buffalo, New York

IT IS GENERALLY RECOGNIZED that the roentgenologic examination of the larynx gives valuable and additional information to the clinical findings. The advantages of this examination are well understood. The volumetric and topographic assessment of lesions can be carried out by anteroposterior and lateral views and vertical laminagrams. The larynx, as a hollow cavity, with its 3-dimensional planes must be evaluated according to its geometric co-ordinates to obtain correct and sufficient information. Clinically, the larynx can be visualized only by laryngoscopy, and only one of these planes can be studied successfully. The roentgenologic approach permits comprehension of the two other planes.

In earlier roentgenologic studies by special methods, the larynx was visualized and outlined by the contact exposure method by Lindgren, by the instillation of opaque oil by Bouchet and Huet, Lemaitre, and Zuppinger, by the technique of Rethi and Waldapfel, and by the displacement of the larynx laterally to the cervical spine during exposure by Smerchinich.

The anteroposterior view of the larynx is considered not very helpful in the evaluation of pathologic conditions, but lateral views (Fig. 1) and vertical laminagrams have proved to be the more promising. Areas of the epiglottis, the pharynx, the pyriform sinuses, and the aryepiglottic folds can be seen and demonstrated in the lateral view. However, the exact site of the disease is often difficult to differentiate because of overlapping and superpositioning of the right and left sides of the larynx. Only the expansion of a tumor, whether anteriorly, posteriorly, or toward the upper larynx can be seen in this positioning. Endolaryngeal lesions are difficult to detect, especially space-consuming processes of the true and false cords, the ventricles of the subglottic area. In addition, the detection of certain lesions of the pharynx, especially of the pyriform sinuses, the aryepiglottic folds, and the region of the arytenoids, is sometimes limited to laryngoscopy. The use of vertical laminagraphy as a technique provides in this group a more exact and reliable method in regard to the topographic condition and the extension of such lesions. Sectional roentgenograms of the larynx are in many respects easier to interpret than conventional soft tissue films. However, as with other diagnostic methods, in roentgenology a knowledge of the technique and roentgen anatomy is important to understand how shadows are produced and to differentiate normal from abnormal. A concept of the anatomy must be regional and 3-dimensional.

The first laminagraphic study of the larynx with special reference to carcinoma of the endolarynx was published by Gunsett (2, 3) in 1937. From that time on, additional fundamental observations of the larynx have been made, describing the physiology and the topography, as well as pathologic conditions of the larynx, as in tumors and in paralysis. In these studies, the value and limitations of this procedure were indicated as related to the difficulties and errors of interpretation. Most of the investigations, however, reported so far were carried out in a small number of cases.

From the Departments of Diagnostic Radiology and Head and Neck Surgery, Roswell Park Memorial Institute, Buffalo.

FIG. 1. Lateral view of the neck showing a large fungating tumor of the epiglottis.

Since the roentgen anatomy of the larynx is well understood, as is its planigraphic appearance, one demonstration of a normal larynx in a healthy patient 35 years of age will outline the structures at the level of the ventricles of the larynx. The films are taken with the patient in a supine position during phonation. Usually 4 to 5 planes, 0.5 or 1 centimeter apart, are obtained which show: the level of the ventricles, the postventricular area, the aryepiglottic region, and the postglottic part of the larynx (Fig. 2).

FIG. 2. Laminagraphic study of a normal larynx. Five sections 0.5 centimeter apart.

Since the larynx is a very mobile structure, the roentgenographic appearance is visible according to the conditions under which the tomographic examination is made during phonation, respiration, or apnea.

From the physiology of the larynx, it is known that its movements are parallel with the direction of the pitch of a note. During a constant equal musical pitch, the kind of the humming vocal plays a definite role. The vocals "o" and "u" produce a lesser and "e" and "i" a greater impulse which is found to produce a larger expansion of the ventricles, the subglottic area, and, partly also, of the pyriform sinuses. This kind of phonation permits a more favorable delineation of the topographic anatomy of the larynx and the endolarynx, respectively. The fact that the larynx is surrounded by cartilage and muscle tends to lend a certain type of mobility to the whole larynx which is best illustrated by deglutition, in which the larynx is brought into contact with its lid, the epiglottis. There is also some upward motion of the larynx during phonation though not so pronounced as in swallowing. The vocal cords make a V-like aperture as seen in relaxation in the usual mirror examination. The posterior edges of the cord tend to approximate themselves in phonation of certain vocals, such as "e" and "i."

TECHNIQUE

The patient lies in the supine position on the laminagraphic table. A multiple cassette, size 10 by 12 inches, which contains either 5 films, 0.5 centimeter apart, or 4 films, 1 centimeter apart, is centered in the region of the thyroid notch (thyroid cartilage). The sections of the larynx are selected approximately either 0.5 centimeter or 1 centimeter apart according to the thickness of the neck from the skin at the level of the thyroid notch. During phonation, the cassette is exposed and 5 or 4 films are obtained at the aforementioned levels. The technical factors are: peak kilovoltage, 60 to 70;

FIG. 3. Laminagram showing edema of the true and false cords with narrowing of the ventricles in a patient with leucoplakia of the cords.

FIG. 4. Laminagram which shows a tumor of the right pyriform sinus with an associated laryngocele on the right.

milliamperage, 50; exposure time, 2 seconds; distance, 40 inches; irradiation dose, 700 milliroentgens measured on the anterior surface of the neck.

The advantages of laminagraphy are: Simple rapid examination of 5 to 10 minutes is possible with good visualization of the endolaryngeal structures including the pyriform sinuses without any summation effect. A slight blurring of the structures is usually noted which can be overlooked as the details in the focal planes are still demonstrated. Also, the amount of radiation received can be disregarded since, with the multiple cassette, only a single exposure is necessary to provide 4 or 5 roentgenograms at different planes. The disadvantages are the special, relatively expensive x-ray unit and the special cassettes which have to be purchased.

MATERIAL AND METHOD

The material consisted of 60 patients seen at this Institute in recent years with a suspected neoplasm of the pharynx or larynx. All patients chosen had had the benefit of roentgenologic examination of the larynx, consisting of both soft tissue studies of the neck and laminagraphic studies of the larynx.

Analysis of the films was made by 2 radiologists without benefit of any clinical information, and their findings were compared with those of the clinician at the time of both direct and indirect laryngoscopy. All cases of neoplasm were proved by biopsy and in many cases were compared with the surgical specimen.

The 60 cases studied were divided into 4 major groups in order to facilitate the analysis. The groups were as follows: (a) cases in which no neoplasm was present; (b) cases in which the neoplasm was primarily in the pharynx; (c) cases which involved the endolaryngeal structures above the level of the cord; (d) cases in which the neoplasm was confined chiefly to the region of the vocal cords.

FIG. 5.

FIG. 5. Laminagram showing a large tumor of the left pyriform sinus extending to the endolarynx.

FIG. 6.

FIG. 6. In the laminagram which was made a large tumor involving both cords with subglottic extension on the right may be seen.

FINDINGS

In an over-all analysis of the 60 cases, it will be noted that, in 30 of the patients, the clinical and roentgenographic findings corresponded with the laminagrams as to the presence or absence of a lesion, and provided no additional information to the clinician. There were 8 patients with benign lesions, and in 4 of these the laminagrams were negative. In the remaining 4 cases, the presence of edema (Fig. 3) indirectly suggested a pathologic process. In 18 cases, the laminagrams did provide further information to the clinician. In 2 of the patients, laryngoceles (Fig. 4), which had been undetected clinically, were demonstrated; and, in 16 cases, the laminagrams demonstrated areas not visualized at laryngoscopy and, thus, showed unseen areas to be normal or demonstrated inferior extension not detected clinically. The roentgenographic findings did not correspond with the clinical findings in only 4 cases—in 3 of these because of unsatisfactory laminagrams and in the fourth because of a false positive diagnosis made from the laminagrams, in which case the false cord with a suspected lesion was proved by laryngoscopy to be normal. The highest percentage of additional information was obtained in the following groups: If the tumor originated or extended beyond the cords in the larynx, it was often technically impossible for the laryngoscopist to see beyond the lesion nor could he be sure of the true condition of the cords or the subglottic region. The laminagrams in these cases were very helpful in demonstrating these unseen areas. Laminagrams were sometimes valuable in large tumors of the pharynx which extended into the endolarynx (Fig. 5) and obscured the clinician's view of the cords. In cases in which the neoplasm was confined chiefly to the region of the cords, the chief value of the laminagrams was the demonstration of subglottic extension (Fig. 6). In the cases in which there was no neoplasm found, as would be expected, there is little additional information which

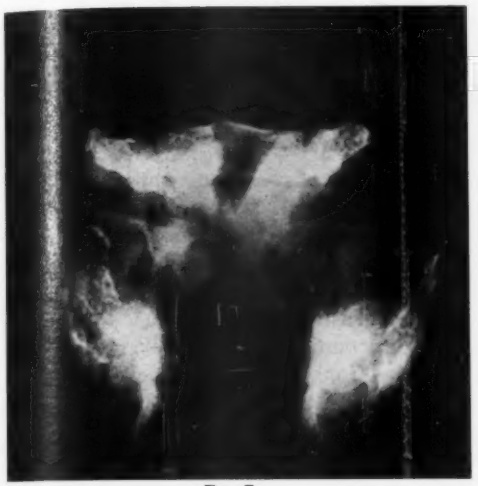


FIG. 7.

FIG. 7. Specimen film of a resected larynx. Cartilage involvement was present but cannot be detected on the films.

FIG. 8. Laminagram showing a carcinoma of the right cord with fixation. Compensatory shift of the left cord similar to that seen in cord paralysis.

FIG. 8.

can be obtained from the laminagrams. In only 1 case of postradiation necrosis in which adequate laryngoscopy was impossible were the laminagrams of further help.

DISCUSSION

Roentgenographic studies of the larynx are not meant to replace laryngoscopy but rather to act as a supplemental diagnostic procedure and to furnish a more objective and permanent record. The limitations of laryngoscopy are well known, as not all lesions are clearly visible and accessible in their entirety. Direct laryngoscopic examination in tumors of the endolarynx is limited in most instances. The upper portion of the tumor can be visualized, but it is usually impossible to pass the scope beyond the tumor and determine the amount of inferior extension. The lateral extent is not so important since the laryngoscopist can see into the region of the pyriform sinuses; and, if these are clear, the lesion is clinically operable. The entire extent of pharyngeal tumors can usually be ascertained by laryngoscopy unless they are very large and extend into the endolarynx.

As has been demonstrated in the class reviewed, a valuable asset in the handling of patients can be obtained by laminagraphic examination with no discomfort or harm to the patient. The added findings by this method apply chiefly to the inferior extent of lesions, for instance, in carcinoma of the cord, which is an important factor when considering a surgical procedure. Also, in larger lesions outside the cord or in the pharynx, this method has proved to be of value, In 2 cases, an unrelated laryngocele was demonstrated which had been undetected clinically. In our experience, the extension of disease along the air passages can be demonstrated, but it is difficult to interpret the absence or presence of involvement of the thyroid cartilage correctly. Asymmetric calcifications or ossifications of this cartilage, especially in older patients, is so haphazard that the information obtained cannot be regarded as informative. Even on some specimen films with pathologic proof

of involvement of the cartilage, the site of invasion could not be accurately demonstrated (Fig. 7) Very small lesions are not detected, as is true in other roentgenographic procedures, but they occasionally manifest their presence by the associated edema which sometimes can be demonstrated by laminagraphy. The relative accuracy of this method with technically precise films is indicated by the occurrence of only one false positive in the 60 cases reviewed.

In the interpretation of the roentgenograms, there are diagnostic difficulties involved. In most instances, it is not possible to make a differential diagnosis on the basis of the laminagraphic examination. Also, the analysis of the roentgenograms does not permit the differentiation of neoplastic infiltration from an inflammatory condition or a benign tumor.

As compared with the irregular density of a tumor, a smooth, rounded appearance of a lesion indicates edema. In come cases, there may be a small tumor undetected on the laminagrams but demonstrating itself indirectly by some associated swelling of a true or false cord. In these cases, a conclusive diagnosis can be made only by laryngoscopy and biopsy. Also, the differentiation of cord paralysis from tumor is sometimes a problem in evaluation. Compensatory changes of the normal cord can occur both in paralysis and in the cord which has been fixed by tumor (Fig. 8), giving the impression that the tumor is on the normal side. The differential diagnosis in these cases may be based again on the irregularity observed in tumors with an additional clue provided by the appearance of the pyriform sinus. In paralysis, there is usually some shortening and a higher position of the pyriform sinus on the involved side which is not noted in the cases of neoplasm. In general, the laminagraphic study should always be combined with a lateral film of the neck, as the extension of the lesion, in regard to its depth or height, is best seen on this view.

SUMMARY

The value of roentgenographic studies of the larynx and pharynx was appraised in 60 patients with suspected neoplasm in these regions. Of these 60 patients, 46 had proved neoplasms. Eighteen in this group of 39 per cent demonstrated observations which were very informative to the clinician in regard to the surgical procedure. No exact differential diagnosis can be expected regarding inflammatory or neoplastic conditions of the larynx and pharynx or involvement of the thyroid cartilage. It was found that the clinical and roentgenographic methods support each other and are indispensable in the correct differential diagnosis of lesions of the pharynx and larynx.

REFERENCES

1. Bouchet, M., and Heut, P. Essai de radiographies frontales du larynx. Ann. otolar., Par., 1938, 50:103-112.
2. Gunsett, A. Ueber die Anwendungsmoeglichkeit der Planigraphie bei Erkrankungen des Kehlkopf-inneren, insbesondere beim Karzinom des Endolarynx. Fortsch. Röntgenstrahl., 1937, 56: 705-713.
3. Gunsett, A., and Schneider, E. Radiographie en coupes frontales du larynx. Bull. Soc. radiol. méd. France, 1937, 25: 569-82.
4. Lemaitre, L. Radiodiagnostic du cancer du larynx. Echo méd. nord, 1925, 3: 1-10.
5. Lindgren, E. Die Roentgen Untersuchung des Larynx. Fortsch. Röntgenstrahl., 1939, 59: 273-285.
6. Rethi, Aurelius. Meine neue Methode bei der Roentgendarstellung des Kehlkopfes und der Luftrohre. Zschr. Laryng., 1914, 6: 28-34.
7. Smerchinich, G. Sagitalaufnahme des Kehlkopfes. Röntgenpraxis, 1941, 13: 277.
8. Waldapfel, Richard. Die roentgenologische Einzeldarstellung des Kehlkopfes. Mschr. Ohrenh., Wien, 1936, 70: 918-928. Zur roentgenologischen Darstellung von Khelkopfkrankheiten. Arch. Ohr. &c. Heilk., 1937, 144: 148-155. Methodik der Roentgenuntersuchung des Kehlkopfes. Leipzig: Georg Thieme, 1938.
9. Zuppinger, A. Die Roentgenuntersuchung bei Pharynx-Tumoren. Fortsch. Röntgenstrahl., 1935, 52: 468-480.

SCIRRHOUS CARCINOMA OF THE COLON AND RECTUM

JAMES C. FAHL, M.D., F.A.C.S., MALCOLM B. DOCKERTY, M.D., and
EDWARD S. JUDD, M.D., F.A.C.S., Rochester, Minnesota

CANCERS ordinarily succeed in destroying their hosts by impeding the functions of the tissues in which they originate or to which they metastasize. These effects are brought about by replacement or displacement by malignant tissue of normal elements that are vital to the organism. In addition to these properties, certain neoplastic cells excite a profound hyperplasia of the connective tissue matrix in which they lie. And while the cells involved in this desmoplastic reaction are not in themselves cytologically malignant, they may actually contribute considerable bulk to the neoplasm which gave them birth, and they may share in major degree in the production of its lethal effects.

To fibrosing cancers of this type the term "scirrhous" has been applied with the connotation that glandular neoplasms, particularly of the breast and stomach, rather than squamous cell cancers or other growths, are the ones which induce the change. "Linitis plastica" is another expression generally employed to designate extensive gastric carcinomas that are of a fibrous or leathery consistency.

Comparable degrees of desmoplasia as an integral part of colorectal carcinomas have been reported but rarely. The accounts of Karstens and Bargen and of Dixon and Stevens concern colonic stenosis secondary to involvement in cases of gastric carcinoma. These reports serve only to emphasize the fact that colonic tissues are capable of sharing in the desmoplastic reaction of linitis plastica.

From the Sections of Surgical Pathology and Surgery, Mayo Clinic, and the Mayo Foundation, Rochester, Minnesota.

Abridgment of thesis submitted by Dr. Fahl to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

Ewing, however, in 1940 observed a scirrhous reaction in a primary colonic carcinoma and attributed it to fibrosis and cicatrization associated with ulceration of a slowly growing and infected surface growth. Reports by Laufman and Saphir, Turnbull, Fisher, and Rosenak, and David comprise the only other available information on primary scirrhous carcinoma of the colon and rectum that we could find in the literature written in English. Since these authors emphasized that a poor prognosis is associated with this type of colorectal neoplasm, it was thought worth while to investigate the clinicopathologic features of scirrhous carcinoma as they appeared in a sizable series of malignant colorectal lesions seen at the Mayo Clinic.

MATERIALS AND METHODS

Permanent microscopic sections from approximately 12,000 surgically resected colorectal carcinomas were screened in a preliminary survey to segregate those which were scirrhous. The starting point was selected as 1930, since many of the gross specimens received prior to that year had been discarded and it was desired to correlate gross and microscopic appearances in a consecutive series. The year 1953 was selected as the "end point" in order to provide a significantly large series and, at the same time, maintain a follow-up period of more than minimal duration. Excluded only were those cases in which the fibrosis could be regarded as a by-product of a previous operation, as an effect of roentgen therapy or of such measures as the injection of hemorrhoids. Accepted for inclusion were those cases in which the lesion exhibited, throughout the area of involvement, strik-

FIG. 1. Scirrhous carcinoma of the rectum, type 1. Note the long sleevelike zone of involvement with absence of ulceration.

ingly greater degrees of fibroblastic proliferation surrounding individual clumps or columns of neoplastic cells than are observed in ordinary carcinomas of the colon and rectum.

As finally evaluated, 91 specimens met the standards for inclusion in this study. Original gross specimens had all been carefully preserved in formalin and were suitable for examination. These were secured and observations made and tabulated with regard to the size, the degree of penetration, and the degree of adherence to neighboring tissues.

Degrees of annularity were correlated with presence or absence of stenosis, and the effect of the latter on the proximal segments was noted. A search was made for positive nodes that had not been removed at the time of the original fresh tissue examination, and the condition of the veins in the vicinity of the growth was scrutinized for indurations that might suggest vascular invasion. Multiple blocks of tissue were taken from the growths and the suspected zones of extension.

The tissues were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and mounted. These slides were added to the original screening collection. Van Gieson's and mucous stains were employed selectively.

FINDINGS

Three different appearances became evident upon examination of the formalin-preserved surgical specimens.

Eleven lesions, hereinafter designated type 1, which were of linitis plastica type, displayed identifying features which were high-lighted by sleevelike involvement of a long segment of bowel, minimal or no gross mucosal ulceration, and local narrowing of the lumen (Fig. 1).

Twenty-nine lesions, designated type 2, displayed a stenosing or napkin-ring type of growth in which the principal characteristics were small size, stony hardness, and a tendency toward annularity. Ulceration was minimal, but obstruction was marked. Proximal segments of bowel were dilated and thick-walled with stercoraceous ulcers present in several instances (Fig. 2).

Fifty-one lesions were classified as type 3. The characterizations of this type of growth were more or less those of ordinary ulcerative adenocarcinomas. Some exhibited unusual degrees of firmness and, in many, cut surfaces of the growths and of their involved regional nodes were unusually white and hard. However, it is doubtful if many of the lesions classified as type 3 could have been singled out from a series of colorectal cancers without recourse to microscopic examination.

The clinical symptoms and signs along with the physical, proctoscopic, and roentgenologic findings in the 91 patients in the series are summarized briefly in Table I. These are presented so that comparisons may be made for the various groups. In the patients with carcinoma of type 1, attention is called to the development of the lesion at a relatively young age, the high incidence of symptoms indicative of obstruction, and the relative infrequency of rectal bleeding as a symptom in spite of the fact that 3 of the patients were suffering from chronic ulcerative colitis.

Among patients with type 2 lesions, the marked emphasis on constipation, abdominal cramps, and abdominal distention points up the obstructive nature of growths of this category.

The lesions of type 3 did not appear to provide sufficient clinical differences from the usual colorectal carcinomas to warrant any special comment.

The preoperative diagnosis was made from the proctoscopic findings in 44 patients, and the presence of a lesion was demonstrated by roentgenographic means in the remainder. Contrast studies using barium furnished the positive roentgenographic evidence except for 10 patients in whom severe degrees of colonic obstruction were verified by plain roentgenograms of the abdomen.

PATHOLOGIC FEATURES

In the preceding section, brief mention was made of certain gross characteristics of these tumors in relation to signs and symptoms. Other gross features deserve brief comment. In the matter of location it appears that except for an absence of type 2, stenosing lesions, in the rectal segment scirrhous carcinomas did not differ from ordinary adenocarcinomas of the colorectum. With respect to size, lesions of type 1 tended to be very large (average volume 150.5 c.c.) and those of type 2 very small (average volume 15.3 c.c.). Those of type 3 exhibited an intermediate range of size, but they were not as large as the average growths in the control series, such as reported by Mayo and Schlicke from this institution. Types 1 and 2 were annular by definition. Almost all lesions in this series were indurated on palpation, and they exhibited a gritty resistance to cutting.

FIG. 2. Scirrhous carcinoma of the sigmoid, type 2. Note the napkin-ring contracture of the involved segment which has been induced by a relatively small growth, showing minimal ulceration.

INHERENT MICROSCOPIC CHARACTERISTICS

Microscopically, as indicated under "Materials and Methods," all of the growths exhibited a degree of desmoplasia far beyond that observed in ordinary carcinomas of the colon and rectum. This reaction was present not only in the central portion of the tumors but in their peritoneal, nodal, and more distant extensions as well. In some, the new and densely formed fibrous tissue encased individual malignant cells or very small cellular aggregates, often with the production of the single-file pattern so familiar in scirrhous carcinomas of the stomach and breast (Fig. 3). In others, indeed in the majority, the fibrous meshwork entrapped large masses of tumor cells which were often disposed in alveolar or glandular arrangement (Fig. 4). The intensity of the fibrous reaction appeared to vary from por-

TABLE I.—CLINICAL FEATURES

	Type of carcinoma			
	1	*2*	*3*	*Total*
No. cases	11	29	51	91
Age, yrs., average	43.7	60.6	57.9	57.0
Range	16–60	22–85	28–79	16–85
Sex,				
Male	5	18	27	50
Female	6	11	24	41
Average duration of symptoms, mos.	12.14	4.74	12.91	11.68
Rectal bleeding	5	8	34	47
Crampy pains	8	28	20	56
Constipation	4	23	17	44
Diarrhea	5	5	12	22
Loss of weight	6	14	24	44
Pounds lost, average	29.4	19.1	18.5	19.95
Rectal mass	7	4	30	41
Abdominal mass	4	7	10	21
Distention	2	29	4	35
Anemia	1	6	8	15
Positive protoscopic findings	6	5	33	44
Positive roentgenologic findings	5	24	18	47

TABLE II.—CORRELATION OF SCIRRHOUS TYPES WITH GRADE OF MALIGNANCY

Broders'	*Type 1*	*Type 2*	*Type 3*	*Total* (91)
Grade 1	0	2	2	4
Grade 2	2	18	28	48
Grade 3	3	7	13	23
Grade 4	6	2	8	16
Total	11	29	51	91

TABLE III.—CLASSIFICATION OF EXTENSION OF SCIRRHOUS TYPE OF ADENOCARCINOMA ACCORDING TO A MODIFICATION OF DUKE'S METHOD

Duke's	*Type 1*	*Type 2*	*Type 3*	*Total*
Type A	0	0	0	0
Type B	1	12	13	26
Type C	10	17	38	65
Total	11	29	51	91

tion to portion within the same tumor, and it was not found feasible to classify the neoplasms on degrees of fibrosis alone. For this reason desmoplasia was considered as a common denominator that might affect the more traditional histologic criteria and the mode and extent of spread of the 91 lesions.

Grade of malignancy (*Table II*). The 4 per cent incidence of lesions of grade 1 (Broders' method) stands in marked contrast to the average of 50 per cent in a series of unselected colonic carcinomas observed at this institution and graded by the same individuals. The 18 per cent incidence of grade 4 in the scirrhous adenocarcinomas stands against an average of 5 per cent in adenocarcinomas in a sizable control series. These findings appear to indicate a reduced ability of well differentiated colorectal malignant lesions to excite a scirrhous reaction as compared with more anaplastic growths. Single filing of malignant cells was a feature found only with grade 4 adenocarcinomas in this series. It is likewise of interest to note that 3 of the 6 grade 4 lesions of scirrhous type 1 occurred in association with chronic ulcerative colitis. The remaining portion of the resected colon did not display any unusual desmoplastic features.

Microscopic extension. Since the majority of the lesions occurred above the peritoneal reflection a modification of Duke's method was employed to classify their extension as follows: type A, growth limited to the intestinal wall; type B, peritoneal or perirectal involvement with "negative" nodes; and type C, positive nodal involvement. Our findings on extension in the group of tumors under discussion are listed in Table III.

Consideration of Table III demonstrates at once that scirrhous growths of the colon and rectum have a marked tendency to penetrate the intestinal wall and to metastasize. None of the growths was limited to the mucosa, and nearly 75 per cent of them were shown to have lymphatic spread. No comparative series is necessary to emphasize the serious implications of the scirrhous facet.

The incidence of involvement of adjacent organs was not greater than that which was observed in an unselected group of colorectal growths.

Neural and perineural involvement. In the present series of cases, random sampling of the growths gave an incidence of 39.5 per cent for neural and perineural invasion. The ominous significance of selective neural and perineural invasion in the life histories of carcinomas in various locations has been well documented. In 1943, Seefeld and Bargen conducted a meticulous search to determine the incidence of such a mode of spread in carcinomas of the rectum. Among the 30 per cent of patients in the group with neural

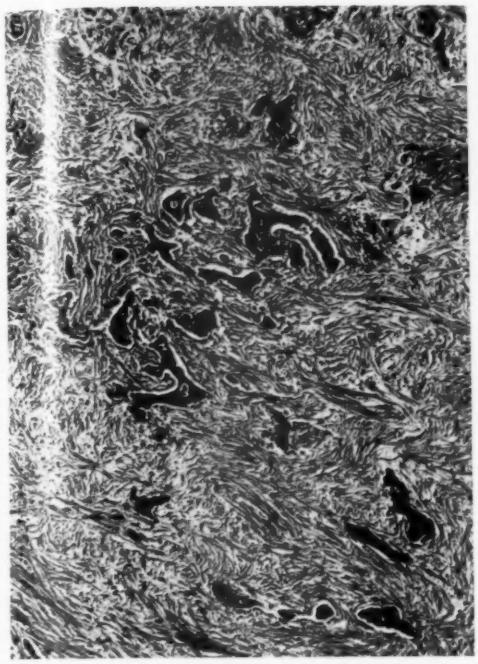


FIG. 3. Grade 4 scirrhous adenocarcinoma of the rectum showing individual cancer cells and small isolated clusters of same encased in a distinctly fibrous matrix. Hematoxylin and eosin, ×65.

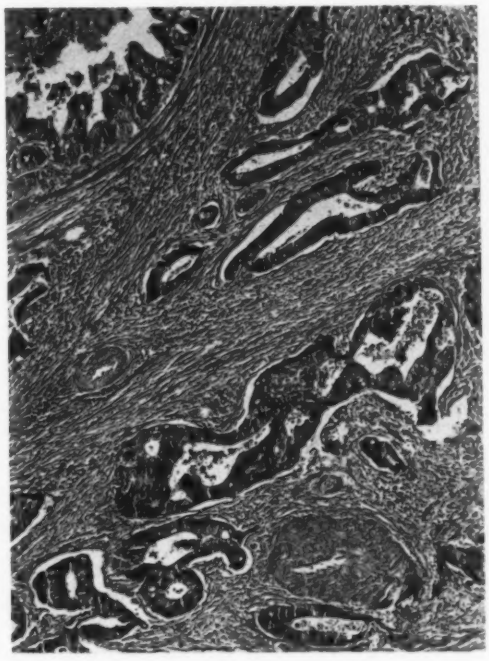


FIG. 4. Metastatic, grade 2, scirrhous adenocarcinoma in a lymph node. Here large aggregates of malignant cells are producing glands everywhere surrounded by dense fibrous tissue. Hematoxylin and eosin, ×65.

and perineural involvement the prediction of a serious outlook was confirmed.

Venous invasion. In a careful analysis of necropsy material, Brown and Warren have established 60 per cent as the incidence for hepatic involvement in the terminal stages of rectal carcinoma. Since the incidence of gross invasion of veins in the vicinity of the lesion in their cases was 100 per cent, the finding at operation of gross or microscopic venous invasion has been accepted as being of serious moment from the standpoint of blood-vascular metastasis. Random sampling of our scirrhous growths revealed venous invasion in 42 per cent (Fig. 5). This figure approximates very closely those obtained by Madison and by Barringer and their associates who conducted studies which were especially designed to give the greatest possible yield for vascular invasion in colorectal growths which were unselected as to type. It is, perhaps, twice as great as that quoted from other comparable series in the literature.

Type 2 lesions herein reported appeared to be the most serious in this regard with an incidence of venous spread of 58.6 per cent.

ASSOCIATED PATHOLOGIC CONDITIONS

Polyps. Two of the 91 patients with scirrhous carcinoma were suffering from congenital polyposis. Eleven others exhibited the presence of 1 or 2 sentinel polyps in the resected segment of bowel. These results are comparable to those which might obtain in an unselected series.

Multiple carcinomas. Six patients in our series suffered from the effects of multiple colonic or rectal cancers; these were synchronous in 4 and metachronous in 2. Such an incidence is not surprising. However, of extreme interest was the fact that only 1 of

the multiple cancers in each case was scirrhous.

Chronic ulcerative colitis. In no less than 5 of the 91 patients scirrhous carcinoma occurred in association with chronic ulcerative colitis. In only 1 of these patients was the colitis clinically active at the time the malignant complication developed. It was originally thought possible that the fibroblastic reaction was a consequence of the background condition. However, in all 5 cases the degree of fibrosis was more intense in the cancer than it was elsewhere. Moreover, only 1 carcinoma in each of the 2 patients who had multiple carcinomas was truly scirrhous. The lesions in 3 of the 5 patients with ulcerative colitis were of the rare type 1, linitis plastica, and in 4 of the 5 the growths were anaplastic, grade 3 or grade 4 on Broders' scale.

Diverticula. These lesions occurred in 8 of the 91 patients, but they were considered unrelated to the carcinoma. In all but 1 case the sacs were found on the resected segment of bowel. Early nonsurgical diverticulitis was found in 1 patient with a scirrhous carcinoma of the right part of the colon.

OPERABILITY

Obviously, since only material obtained at resections was chosen for our study, no statements can be made concerning the over-all operability of scirrhous cancer of the colon and rectum. The authors have the distinct impression that the operability rate is low, as compared with that for nonscirrhous carcinomas of the colon.

In 26 per cent of the total there was evidence of such degrees of visceral metastasis at laparotomy that resection was strictly palliative. In only 6 of the 11 patients with type 1 lesions was the lesion resected with hope of cure. Operative mortality was 3.3 per cent.

OUTLOOK FOR PATIENTS

Since the series is a small one and since a significant time has not elapsed in all cases since operation, the data with respect to the outlook for patients lack the significance of other series. However, analysis of even the short term trends is worth recording. Only 3 of 11 patients with type 1 lesions, linitis plastica, are still alive. One of these patients represents a 79 month cure, but the other 2 had palliative resections and are currently carrying metastatic or recurrent carcinomatous deposits.

Twenty-seven of the 29 patients with type 2 lesions have been followed-up for short periods. Only 12 of these 27 are known to be living and 5 have residual carcinoma. Only 15 of the 48 patients with type 3 lesions whose courses have been followed were alive at the completion of the study. Four of these 15 patients were suffering from the effects of recurrent or metastatic disease.

COMMENT

Scirrhous adenocarcinoma of the colon and rectum is a rarely encountered lesion. As herein defined, it comprised only about 1 per cent of the colorectal lesions coming to resection. Although featuring a good correlation with intestinal obstruction, a tendency perhaps toward occurrence as a complication of chronic ulcerative colitis, and, in cases of type 1 lesions a tendency to occur at an early age, the entity is clearly pathologic rather than clinical. In other words, the preceding data in no way allow definition of the scirrhous type preoperatively.

Pathologically, the cause of the scirrhous reaction remains unexplained. Extrinsic factors such as irradiation and the injection of sclerosing solutions were excluded in this study. Infection has not been a significant factor. The majority of the patients were afebrile; they had normal leucocyte counts and minimal inflammatory reactions in the carcinomas. Even the carcinomas which complicated chronic ulcerative colitis occurred in segments which elsewhere displayed nothing unusual by way of excessive scarring. Moreover, in the "multiple cancer" category only one of the growths displayed the characteristic desmoplasia in each case. An additional factor militating against a

primary and local change in the host as being the cause of the fibrosis was the universal desmoplasia observed in metastatic deposits from scirrhous adenocarcinomas studied in our series. Briefly, therefore, the scirrhous reaction appeared to be induced by some characteristic inherent in the carcinomas themselves.

It seemed rather paradoxic to us that a fibrosing reaction, far from containing the malignant elements which it enmeshed, seemed to promote their dissemination. In this regard, some experimental evidence appears to be pertinent.

Simpson, working with transplantable but nonmetastasizing squamous cell cancer in mice, was able to induce generalized dissemination by injection of crude testicular extract with tumor tissue. He expressed the belief that the mucolytic enzymes of the embryonic testicular cells introduced the necessary "spreading factor." Bensley, using the same type of extract, induced an acceleration in the growth and development of fibroblasts with a rapid shift to dense collagenous connective tissue. Viewed in the light of these experiments, a sequence can be constructed in which certain undifferentiated cancer cells acquire the ability to produce potent mucolytic enzymes that facilitate local invasion and metastasis and, secondarily, incite the surrounding connective tissue cells to produce a dense fibrous network about the cancer. On this basis, desmoplasia appears to correlate positively with the observed high incidence of anaplastic lesions in our series of cases.

The scirrhous reaction introduced still another factor which in our opinion contributed to the clinical aggressiveness of these lesions. By this we refer to the factor of obstruction, a major item in 30 per cent of our 91 patients.

Nickell and Dockerty found that 25.7 per cent of completely obstructing resectable cancers of the left half of the colon yielded 5 year survivals in contrast to a survival rate of 51.7 per cent for lesions which were nonobstructing or partially obstructing.

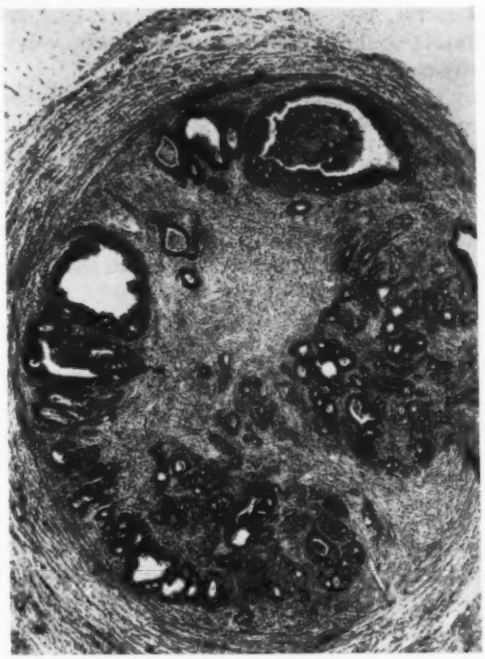


FIG. 5. Grade 2 adenocarcinoma invading a pericolonic vein. Fibrosis and hyalinization are readily apparent in the clot which is organizing about the cancerous acini. Hematoxylin and eosin, ×25.

Wilder similarly noted that completely obstructing but resectable carcinomas of the right half of the colon reduced to 23 per cent the 5 year survival rate of patients, whereas 75 per cent of those who did not have obstructive lesions achieved this goal. The poor survival rate in these two series of obstructing lesions, as in ours, may have been related to the milking action of hyperperistalsis in the dislodgment of cells and their propulsion along venous and lymphatic channels leading away from the growth.

SUMMARY AND CONCLUSIONS

Ninety-one cases of primary scirrhous adenocarcinoma of the colon and rectum have been studied clinicopathologically. Three pathologic prototypes were delineated: In 11 cases the lesions presented the rare "linitis-plastica" type of configuration; in 29 they were stenosing "napkin-ring"

cancers, and in 51, ulcerative growths definable only on the basis of microscopic evidence of pronounced desmoplasia.

The scirrhous reaction appeared to be excited by the neoplastic cells themselves. It seemed to be a property possessed principally by certain anaplastic tumors, the involved lymph nodes and visceral metastatic lesions which maintained the scirrhous pattern. Other primary cancers in the same hosts were never desmoplastic.

The growths were unusually aggressive. Perineural and venous involvement was frequently observed, nodes were often invaded, and a high incidence of hepatic metastasis limited many resections to the palliative category. The average small size of the growths is paradoxic in this over-all picture.

A completely accurate prediction of results of treatment was not possible from this small series. The trend indicated, however, is disappointing.

REFERENCES

1. Barringer, P. L., Dockerty, M. B., Waugh, J. M., and Bargen, J. A. Carcinoma of the large intestine; a new approach to the study of venous spread. Surg. Gyn. Obst., 1954, 98: 62–72.
2. Bensley, Sylvia, H. Histological studies of the reactions of cells and intercellular substances of loose connective tissue to the spreading factor of testicular extracts. Ann. N. York Acad. Sc., 1950, 52: 983–989.
3. Brown, C. E., and Warren, Shields. Visceral metastasis from rectal carcinoma. Surg. Gyn. Obst., 1938, 66: 611–621.
4. David, V. C. Malignancy in linitis plastica. Surg. Clin. N. America, 1931, 11: 47–56.
5. Dixon, C. F., and Stevens, G. A. Carcinoma of linitis plastica type involving the intestine. Ann. Surg., 1936, 103: 263–272.
6. Ewing, James. Neoplastic Diseases; a Treatise on Tumors. 4th ed. Philadelphia: W. B. Saunders Co., 1940.
7. Karstens, H. C., and Bargen, J. A. Carcinoma of the colon simulating linitis plastica. Proc. Mayo Clin., 1944, 22: 231–235.
8. Laufman, H., and Saphir, O. Primary linitis plastica type of carcinoma of the colon. Arch. Surg., 1951, 62: 79–91.
9. Madison, M. S., Dockerty, M. B., and Waugh, J. M. Venous invasion in carcinoma of the rectum as evidenced by venous radiography. Surg. Gyn. Obst., 1954, 99: 170–178.
10. Mayo, C. W., and Schlicke, C. P. End-to-end ileocolostomy; indications for, and evaluation of, in resection of right portion of colon in one stage for malignant lesions. Surgery, 1942, 12: 716–728.
11. Nickell, D. F., and Dockerty, M. B. Five year survival rate in cases of completely obstructing annular carcinoma of descending colon and sigmoid; pathologic study. Surg. Gyn. Obst., 1948, 87: 519–524.
12. Seefeld, P. H., and Bargen, J. A. The spread of carcinoma of the rectum; invasion of lymphatics, veins, and nerves. Ann. Surg., 1943, 118: 76–90.
13. Simpson, W. L. Mucolytic enzymes and invasion by carcinoma. Ann. N. York Acad. Sc., 1950, 52: 1125–1132.
14. Turnbull, R. B., Fisher, E. R., and Rosenak, B. D. Primary linitis plastica carcinoma of colon. Cleveland Clin. Q., 1951, 18: 210–216.
15. Wilder, T. C. Obstructing carcinoma of the right colon. Thesis, Graduate School, University of Minnesota, 1948.

FIBROSARCOMA OF THE THYROID GLAND

V. L. CHESKY, M.D., F.A.C.S., C. A. HELLWIG, M.D., F.C.A.P., and
J. W. WELCH, M.D., Halstead, Kansas

IN SWITZERLAND, about one fifth of all malignant goiters are classified as sarcomas, according to Walthard; in our country Ewing's standpoint, that the occurrence of true sarcoma of the thyroid still requires demonstration, is generally accepted.

We intend to show that Ewing's position is too radical and that there is a well characterized type of sarcoma which by special stains can be clearly differentiated from epithelial neoplasms. We regard at least 4 cases reported from this country as definitely established and we would like to add 4 cases of our own material.

Among 628 malignant goiters removed at the Hertzler Clinic during the last 40 years, 4 tumors were found which conformed to the strictest morphologic requirements to be regarded as true fibrosarcomas of the thyroid gland.

There were 3 female patients, 33, 53, and 58 years old, respectively, and a 70 year old male. In the youngest patient the tumor developed 2 years after removal of a benign nodular goiter, whereas the other patients had noticed a rapid growth of a long-standing goiter. Only 1 patient, the 70 year old man, had noticed weight loss of 14 pounds during the previous 2 years. Two patients complained of choking sensation and difficulty in swallowing. The clinical diagnosis was benign nodular goiter in 3 cases; in the oldest patient the tumor in the neck was so hard, immovable, and firmly attached to the trachea that a malignant lesion was suspected.

Bilateral thyroidectomy was performed on the 3 female patients, but in the oldest patient only a portion of the tumor pressing on the trachea could be removed, and a tracheotomy was carried out. He died from bronchopneumonia 1 week after operation.

Our 33 year old patient is at present alive and without evidence of disease 21 years after removal of her tumor; the other 2 female patients died less than 1 year after operation. Autopsy was performed on 1 of them and revealed multiple metastases in the lungs and intestinal tract.

From the Hertzler Clinic and Research Foundation, Halstead.

PATHOLOGY

The size of the surgical specimens varied from 4.5 to 8 centimeters. The thyroid tissue was diffusely invaded, but in only 1 case were surrounding neck structures invaded. The cut surface of these tumors was whitish in color and the consistency was very hard (Fig. 1).

Microscopic examination of many sections of each tumor did not reveal any transition of epithelial cells into spindle cells (Fig. 2). Thyroid follicles, when present, were lined with entirely inactive cells. The tumor cells were of spindle shape, and there was more or less variation in their size and form, but never as marked as in spindle cell carcinoma of the thyroid. Mitotic figures were encountered here and there, but giant cells were not present. The spaces between the cells were crossed by coarse and fine fibers (Fig. 3). Individual cells were surrounded by collagenous fibers, and delicate fibrils were seen attached to tumor cells. Many cells tapered off at the end, terminating in wavy fibrils (Fig. 5). Never were groups of cells observed lying closely together and surrounded with a fibrous stroma, as is characteristic of epithelial neoplasms.

The spindle cells were arranged in strands tending to interlace, running in various

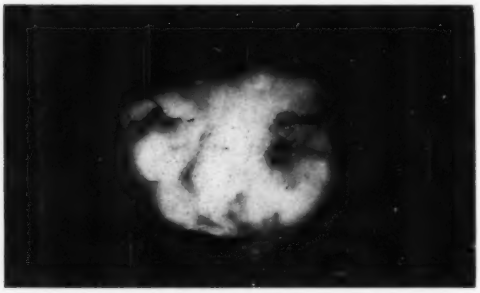


FIG. 1. Piece of thyroid sarcoma removed from anterior wall of trachea of 70 year old man, showing whitish cut surface.

directions and producing a whorled effect (Fig. 4). Of the specific stains for collagenous fibers, Gallego's fuchsin iron stain appeared to be the most helpful in revealing the nature of the fibroblastic sarcomas.

DISCUSSION

That fibrosarcoma of the thyroid is not nearly so frequent as reported in the earlier literature is quite true, but there is no reason why a neoplasm should not arise from the connective tissue elements of the thyroid as from any other organ.

Zeckwer regards as authentic sarcomas the 3 cases reported by Woelfler and the 1 case each reported by Mueller and Speese, Tiffany-Lamier, and Saltykow. Zeckwer's own case would be classified by European pathologists as polymorphous cell sarcoma and in our country it would be known as giant cell carcinoma.

Meeker regards 2 cases reported from this country as definitely established sarcomas, namely Vandenberg's and Binnie's. The histologic diagnosis in these 2 cases was made by Warthin and Welch. Meeker's own case was observed in a 16 year old girl with a very large tumor weighing 255 grams. The patient survived the operation only a short time. Microscopic examination showed the tumor cells arranged in bundles and appearing in longitudinal, transverse, and oblique sections. The photomicrographs from tumor sections stained with Mallory's and Maresch-Bielschowsky's stain leave no doubt of the fibrosarcomatous structure of Meeker's tumor.

DeQuervain, in Switzerland, found among his 200 malignant goiters 10, 5 per cent, which had the microscopic structure of fibrosarcoma. Wegelin (11) agreed with the histologic diagnosis. He pointed out that he has never observed bone metastases in sarcoma of the thyroid, in contradistinction to their frequency in carcinoma. The most common site of metastases in Wegelin's large material of thyroid sarcoma was in the lungs.

The relative frequency of thyroid sarcomas in countries of high goiter endemicity as compared to our country cannot be attributed to less critical diagnoses of European pathologists. More plausible appears to be the explanation offered by Walthard that sarcoma of the thyroid originates, as a rule, in fetal adenomas which are more

TABLE I.—DATA FROM 4 CASES OF FIBROSARCOMA OF THE THYROID

Case No. Age, yrs. Sex	*Symptoms*	*Preop. diag.*	*Operation*	*Roentgen therapy*	*Follow-up*
1 58 F	Goiter 25 yrs. Roentgen ray treat. 15 yrs. ago. Rapid growth past 6 mos.	Bilat. nodular goiter	5–12–27, bilat. subtotal thyroidectomy	Postoperative	Dysphagia, 3 wks. after roentgen ray treatment. Died 6–16–27
2 53 F	Dyspnea. Goiter noticed for 2 years	Nodular goiter	5–12–29, bilat. subtotal thyroidectomy		Died 6–19–29. Autopsy, metastases to lung, intestines
3 70 M	Throat trouble 15 yrs. Shortness of breath, dysphagia 6 weeks	Cancer of thyroid	8–5–29, mass overlying trachea removed, tracheotomy		Died 8–12–29, postoperative bronchopneumonia
4 33 F	Benign goiter Nov. 1936. Recurrence, Jan. 1939	Recurrent nodular goiter	11–29–36, bilat. subtotal thyroidectomy. 1939, removal recurrence		1959, living without evidence of disease

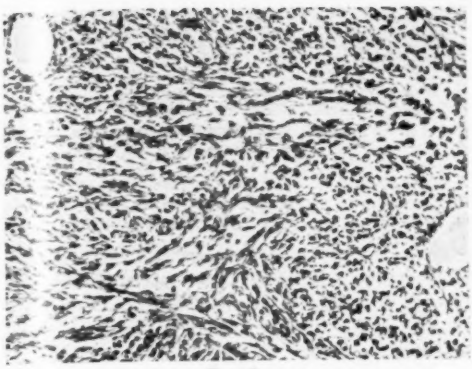


FIG. 2.

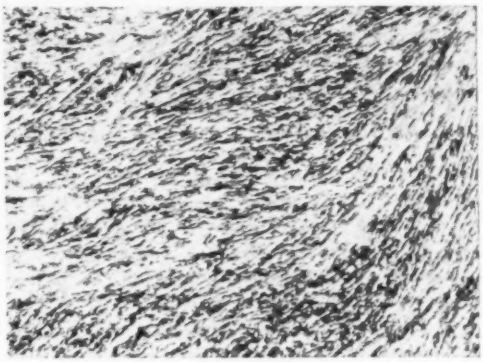


FIG. 3.

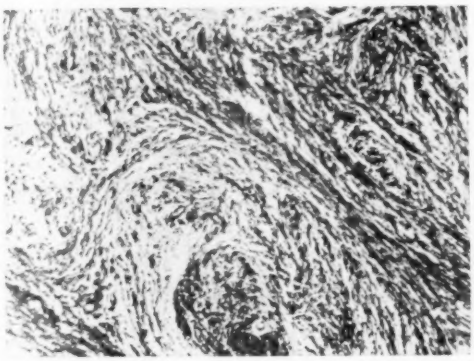


FIG. 4.

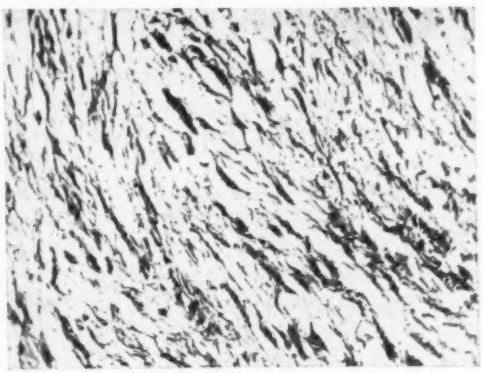


FIG. 5.

FIG. 2. Fibrosarcoma of thyroid in 58 year old female. The two thyroid follicles are lined with inactive cells and there is no transition of epithelial cells into spindle cells.

FIG. 3. Microscopic section of same tumor shows coarse and fine fibers between tumor cells.

FIG. 4. Tumor section of only surviving patient with fibrosarcoma. The bundles of spindle cells and collagenous fibers tend to interlace, producing a whorled effect.

FIG. 5. Higher magnification of same tumor shows tumor cells tapering off at the end and terminating in wavy fibrils. Gallego stain.

common in countries of high goiter endemicity. Wegelin (12) pointed out that he has observed young, extremely cellular, fibroblastic tissue in fetal adenomas with hemorrhage or inflammatory changes. These areas, according to Wegelin, are histologically almost indistinguishable from early sarcoma. Gatti has described 1 case of thyroid sarcoma associated with streptococcic infection of an old adenoma. Wegelin believes that such regenerative inflammatory proliferations of connective tissue may develop into a sarcomatous neoplasm.

CONCLUSIONS

During a 40 year period, among 628 malignant goiters, 4 tumors were observed which conformed to the strictest requirements to be regarded as true spindle cell sarcomas.

Four cases previously reported from this country must be regarded as definitely established sarcomas.

The difference in the relative frequency of thyroid sarcomas in countries of high goiter endemicity as compared to their rarity in this country can be explained by the fact

that fibrosarcoma develops as a rule in fetal adenomas, which are common in severely endemic goiter regions of the world but have been found to be very rare in North America.

REFERENCES

1. Binnie, J. F. Malignant neoplasms of the thyroid with metastases in the intestine and in bone. Surg. Gyn. Obst., 1918, 26: 288.
2. DeQuervain, F. Die Struma maligna. Neue Deutsche Chir. Stuttgart: Enke Verlag, 1941.
3. Ewing, J. Neoplastic Diseases. 4th ed. Philadelphia and London: W. B. Saunders Co., 1940.
4. Gatti, G. Sarcome de la thyroide; rapide développement à la suite d'infection par le streptocoque pyogène. Rev. chir., Par., 1895, 15: 618.
5. Meeker, L. H. A case of spindle cell fibroblastic sarcoma of the thyroid gland. Proc. N. York Path. Soc., 1952, 22: 51.
6. Mueller, G. P., and Speese, J. Malignant disease of the thyroid gland. Univ. Pennsylvania. M. Bull., 1906–1907, 19: 74.
7. Saltykow, S., Ueber das gleichzeitige Vorkommen des Sarcoms und des Carcinoms in der Schilddruese. Zbl. allg. Path., 1905, 16: 547.
8. Tiffany, L. M., and Lamier, B. B. Primary sarcoma of the thyroid gland. Ann. Surg., 1897, 26: 498.
9. Vandenberg, H. J. Report of a case of sarcoma of the thyroid. J. Michigan M. Soc., 1917, 16: 18.
10. Walthard, B. Formenkreise und Zusammenhaenge von Kropf und Krebs. Strahlentherapie, 1955, 34: 69.
11. Wegelin, C. Die Schilddruese. In Henke, F., and Lubarsch, O. Handbuch der spec. Path. & Histologie. Vol. VIII. Berlin: Springer-Verlag, 1926.
12. Idem. Malignant disease of the thyroid gland and its relation to goitre in man and animals. Cancer Rev., Brist., 1928, 21: 297.
13. Woelfler, A. Ueber die Entwicklung und den Bau des Kropfes. Arch. klin. Chir., 1883, 29: 754.
14. Zeckwer, J. J. Fibrosarcoma of the thyroid. Arch. Surg., 1926, 12: 561.

FACTORS AFFECTING THE MORTALITY FROM ACUTE GASTRODUODENAL PERFORATION

FRANK A. ROGERS, M.D., F.A.C.S., Whittier, California

THE PRESENT STUDY summarizes information on a group of patients treated for acute perforated ulcer on one surgical service of the Los Angeles County General Hospital during the years 1944 to 1959. An attempt was made to survey a representative body of clinical material in search for areas in which emphasis on careful management might result in an improved record of survival. Factors were sought which substantially affected the mortality from this complication of peptic ulcer disease.

The 1,000 patients studied were admitted to one general surgical service with confirmed gastric, duodenal, or pyloric perforations seen at operation or postmortem examination. The College of Medical Evangelists' Surgical Service averages 7 surgical admissions per day. Slightly over 50 per cent of the patients require operation, and 25 per cent of patients admitted need emergency surgical procedures. One of every 40 patients treated has had a perforated peptic ulcer.

This incidence of peptic ulcer may be similar to that in the population at large, although a steadily increasing number of ulcers among Negroes has been noted in recent years, and in this race perforated ulcer occurs half as frequently as in Caucasians (2). In one recent 14 year period slightly less than 900,000 patients were hospitalized, from which approximately 9,000 cases of peptic ulcer were coded. Sixteen per cent of these had perforated and, of this group, approximately 20 per cent were perforated gastric ulcers—an over-all ratio of duodenal to gastric of 4 to 1.

Whereas the general mortality for this surgical service averages about 7 per cent, the mortality for perforated ulcer has remained relatively high. The gross mortality rate, which includes both deaths in patients operated upon and deaths occurring in moribund or undiagnosed patients not operated upon, continues to be about 16 per cent. The operative mortality was 10.5 per cent.

Factors affecting chances of survival from gastric or duodenal perforations are multiple and interrelated. Age, sex, duration of the perforation prior to closure, size and location of the perforation, the presence of severe associated disease, and preoperative and postoperative complications have great influence on the mortality rate. The significance of correct diagnosis and, in some instances, operative techniques play important roles. A discussion of these various factors and their influence on the group studied is presented.

SEX

The great majority of patients were males. There were 879 males and 121 females—an 8 to 1 ratio. One of the most significant findings in this study is the greatly increased mortality for females. Although less frequently afflicted, females show a mortality rate twice that for males, 28 per cent to 14 per cent, respectively. In the group operated upon the female mortality was 18 per cent and that for males only 9 per cent. Many patients died without operation, and in this group again the increased virulence of the disease in women is noted with a fatality rate of 12.5 per cent as compared with 5.5 per cent for men.

The reasons for the increased severity of this disease in females is not easily explained.

From the Surgical Service of the College of Medical Evangelists School of Medicine, Los Angeles.

TABLE I.—RELATION BETWEEN SIZE OF PERFORATION AND MORTALITY IN DUODENAL AND GASTRIC ULCER PATIENTS

Size	*No. of cases*	*No. of deaths*	*Mortality, per cent*
1–3 mm.	324	20	6
3–5 mm.	266	28	10.5
5–7 mm.	60	9	15
7–10 mm.	96	25	26
1–2 cm.	125	44	34
Over 2 cm.	42	18	43
Total	913	144	

TABLE II.—RELATION BETWEEN DURATION OF PERFORATION AND MORTALITY

Duration, hours	*No. of cases*	*Mortality, per cent*
0–8	347	8
8–16	431	9
16–24	106	22
24–48	64	26
Over 48	52	47
Total	1,000	

TABLE III.—RELATION BETWEEN MORTALITY AND FLUID SPILL

Spill	*No. of cases*	*No. of deaths*	*Mortality, per cent*
Small	358	21	6
Moderate	327	30	9
Large	224	38	17
Massive	91	50	55
	1,000	139	

One partial explanation is suggested by the ages of female patients which average 3 to 5 years older than the males'. The age difference widens more in the group with gastric perforation in which mortality from perforation is higher (26 per cent) than for duodenal perforation and in which there is a relative increase in the number of female patients. A further explanation is provided by taking into account the increased number of elderly females undiagnosed or too ill to be operated upon. The heightened mortality for females as seen in this survey serves to emphasize the need for increased diligence in treatment of this sex.

AGE

Age probably has the greatest single influence on the chances of survival from perforated ulcer. Its association with other factors influencing mortality, such as the presence of multiple associated diseases, makes the problem of analysis more difficult. In this hospital over 60 per cent of perforations occur in patients in the fifth to eighth decades. In addition, the highest incidence of perforation has shifted nearly 1 decade later during the period of the past 10 years.

Although perforated peptic ulcer occurs in males generally 8 times more often than it does in females, this ratio, too, appears to be changing. Among a large group of patients studied shortly after 1941 there were 17 times more males than females. Ten years later this ratio was 8 to 1. Age, however, has an important and specific influence on the sex ratio, for in perforations in the young —those in the second and third decades— the ratio is 16 males to 1 female. In the aged patient the ratio has been only 4 males to 1 female. The average age for females with both perforated gastric and duodenal ulcers is greater than that for the male group.

As is shown in Figure 1, it is from the groups of patients more than 50 years old that perforated peptic ulcer takes a steeply rising toll. Shock, hemorrhage, and other complications are potentially lethal to all but are even more so at the ages when degenerative diseases are already present to weaken the patient's resistance to any acute episode.

SIZE OF PERFORATION

The majority of perforated duodenal ulcers are less than 5 millimeters in diameter. The average gastric perforation is larger. The size of the ulcer perforation does have prognostic significance, for the mortality increases steadily from 6 per cent to 43 per cent as the size of the perforation increases from 1 millimeter to more than 2 centimeters. To a degree, the size of the opening determines the massiveness of the assault on the peritoneum by the contents of the stomach and duodenum. In patients found to have large amounts of peritoneal fluid, almost invariably the factors of a late admission and a large perforation were also noted. An interesting relationship between the size of the perforation and resultant

mortality in this group of patients was noted (Table I). For perforations 5 millimeters or less in diameter, the mortality remained below 20 per cent. The mortality for the total group of 1,000 patients increased steadily as the size of the perforation increased, reaching 43 per cent for perforations of more than 2 centimeters in diameter. When these cases were separated into duodenal and gastric groups the results were approximately the same for perforations up to 1 centimeter in diameter. For larger perforations the mortality from gastric ulcer rose more rapidly than that from duodenal, reaching 43 per cent.

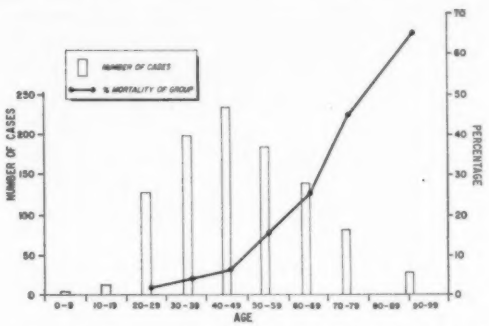


FIG. 1. Deaths resulting from perforated duodenal ulcers.

DURATION OF PERFORATION

Perforation of a peptic ulcer is usually such a dramatic event that in most cases it is easy to determine the exact length of time between the occurrence of the perforation and its operative closure. Over the years at this hospital, there has been no change in the speed with which the patients are admitted to the hospital. Seventy per cent are seen in the admitting room within 6 hours after the perforation and 16 per cent are admitted 12 hours afterwards.

Although more than 60 per cent of the patients are admitted within 6 hours, only 40 per cent have had the perforation closed within 8 hours. During recent years there has been a lengthening of the time between admission of the patient and closure of the ulcer, although the accuracy of diagnosis has not diminished. In some instances additional time has been taken to more adequately prepare the patient. The interval between perforation and closure of the ulcer and the mortality rate rise from 8 per cent at 0 to 8 hours to 47 per cent after 48 hours (Table II). The sharply rising death toll among patients whose treatment was begun 16 hours or more after perforation is notable. A majority of deaths in this study were in patients admitted late with duodenal ulcer. This factor is a very important one in the determination of mortality from this disease and ranks closely with the presence or absence of shock as a determinant of both morbidity and mortality. In a few instances, patients have already been in the hospital for treatment of such diseases as cerebral artery thrombosis or hemorrhage, malignant lesions, or genitourinary dysfunction and have suffered perforation. These patients are included in the early admission category but have a high fatality rate and thus serve to keep the mortality higher than it would normally be among patients whose perforations are closed early.

FLUID SPILL

Another factor affecting results of treatment for perforated peptic ulcer is the amount of peritoneal fluid found at operation. Large or massive amounts are indicative of a poor outlook. Arbitrary divisions of small, moderate, large, and massive amounts were set up. A large spill was interpreted as an estimated amount of peritoneal fluid between 500 and 1,000 cubic centimeters and massive amounts were considered to be over 1,000 cubic centimeters of free peritoneal fluid. Table III shows the marked rise in fatality associated with a large or massive fluid spill. From 6 per cent mortality in patients with small spill, the figure rises steadily to 55 per cent mortality in patients with massive spill. The majority of patients have small to moderate amounts of fluid in the abdominal cavity at the time of operation. In the earlier stages of perforation much of the peritoneal fluid represents

contents of the stomach and duodenum. Later on, depending on how much more fluid is ingested by the patient, a relatively greater amount of fluid is contributed by the peritoneum in response to chemical and bacterial irritation. The amount of peritoneal fluid increases as the duration of perforation prior to the time of closure lengthens.

Twenty-two per cent of these patients were classed as having large amounts of fluid and in 9 per cent the amount was voluminous. In the latter category the mortality rose to 55 per cent. The mortality rates were essentially the same in patients with either duodenal or gastric ulcer perforations. There was a relatively larger number of gastric ulcer patients with large and massive amounts of fluid.

Although interesting, this study of fluid spill is not in itself a direct factor affecting the fatality rate from gastroduodenal perforation but is a feature produced by the larger perforations which remain open longer. While of significance in prognosis, it relates primarily to the duration of perforation as well as to the size of the perforation.

ASSOCIATED DISEASES

Another factor of considerable importance, particularly among the group of patients being reported, is the incidence of concomitant serious illnesses. In virtually every case ending fatally there was at least one and often a combination of associated diseases of a severe nature adding to the problems of the case. Approximately 1 of every 7 patients with perforated gastroduodenal ulcer had one or more serious associated diseases which required additional considerations in treatment and were factors adding to the over-all risk. The advanced age of many of the patients accounts for the high incidence of multiple diseases. In the group of 146 patients with concomitant disease processes, such as recent myocardial infarction, pneumonia, hypertension, degenerative central nervous system disease, malignant lesions, chronic alcoholism, advanced emphysema and other disorders, the mortality reached 50 per cent. The frequent association of alcoholism and ulcerative disease should be emphasized. In his efforts to close the perforation, the surgeon must not overlook associated diseases as factors affecting the general mortality.

HEMORRHAGE

One of the most severe complications of gastroduodenal perforations is hemorrhage. The incidence of significant hemorrhage is frequently not fully appreciated. Recent reports place the incidence of bleeding between 12 and 20 per cent. Bleeding manifested usually as melena but also frequently by both hematemesis and melena occurred in 1 of every 7 cases (14 per cent) in the present series. In the group with perforated ulcer and severe hemorrhage the mortality reached 60 per cent. A further observation lending weight to the importance of preoperative or postoperative blood loss is the fact that massive and continued hemorrhage was a contributing factor in 22 per cent of the deaths in this series.

In many of the patients, but by no means all, the source of the hemorrhage was a separate ulcer either in the posterior duodenum or in the stomach, usually along the lesser curvature. In many other cases, very large ulcers, some involving most of the circumference of the first portion of the duodenum, were found which both perforated and bled.

SHOCK

Shock was the most commonly occurring complication in the group of patients under study. The presence of shock in the patient with perforated ulcer is not only of grave prognostic significance but in many cases it is inadequately treated. It is in this area that great emphasis must be made not only on seeking out all of the possible factors that may cause the shock, but also on expeditiously correcting these factors and stabilizing the patient prior to any surgical pro-

cedure. Operation must be delayed until adequate circulating blood volume has been established and the blood pressure truly stabilized. The urgency for blood and fluid replacement and pressure and pulse stabilization outweighs, in this group, the importance of early operation. The hypotension should be corrected, if possible without vasopressors, and a urine output of 40 to 50 cubic centimeters per hour should be established before operation is undertaken. This emphasis on concentrated attention to shock is in agreement with the practical step by step procedure of management outlined recently by Berne and Mikkelsen and based largely on experience with patients at this general hospital.

Patients who were admitted with a significant element of hypotension were frequently seen late after perforation and tended to be in older age groups, the origin of shock arising from multiple sources. This complex picture in the aged group is associated with a reduced efficiency of the cardiovascular and ventilatory systems. In many cases the hypotension can be related to the onslaught of digestive juices on the peritoneum where the factors of pain and, later, fluid loss are at work. As the disease progresses, there is a tremendous outpouring of fluid, not necessarily all as free peritoneal fluid, but a good deal as plasma loss into the irritated and exposed intra-abdominal surfaces. A hypovolemia is produced that may or may not be clinically appreciated. Particularly in the elderly and those ill from other acute and chronic degenerative diseases, is it probable that normal body mechanisms will not be able to compensate adequately for this acute loss. As time elapses, the factor of sepsis is added and the splinted abdominal wall and reduced diaphragmatic motion further compound the abnormal physiologic condition which is already present.

In many of the cases summarized here the most vigorous treatment for shock failed. Large amounts of blood, plasma, and electrolytes were given without adequate response. Among the charts of patients whose cases ended fatally the comments "never out of shock" and "progressive shock" are repetitive. In several cases shock noted preoperatively continued or recurred in the immediate postoperative period despite what appeared to be good replacement therapy. Hydrocortisone was used frequently, but rarely if ever appeared to alter the shock picture.

The most common fault in combating shock in this type of patient is the failure to comprehend fully the relative and absolute deficits that can occur in blood volume. Blood or plasma or both may be needed, depending upon the individual. The volume of fluid required to revive some of the more severely depleted patients may actually exceed that lost. In addition to the large amounts of plasma and electrolyte fluid pooled within the abdominal cavity, the vascular bed generally expands. With the venous pressure and lungs carefully monitored, replacement therapy can be pushed until the venous pressure begins to rise. Without adequate and prompt treatment of shock certain abnormalities in the cardiovascular, pulmonary, and renal systems compound to reach a point of irreversibility. It is in this area of treatment that some inroads can be made toward improving the results of the treatment for perforated ulcer.

DIAGNOSIS

The diagnosis of perforated peptic ulcer is usually not difficult and was correctly made in over 95 per cent of these cases. Over 85 per cent of the patients gave a definite past history of peptic ulcer or related symptoms compatible with that diagnosis. Sixty patients had already had perforations. There remain, however, a small number of patients, usually chronically ill and aged, who reach medical care late. Their histories are poor and findings less dramatic, being masked by the presence of abdominal fluid, occasionally cushioned by a pneumoperitoneum, and often blurred by shock. A few cases were misdiagnosed and

the patients were sent initially to nonsurgical wards where they deteriorated further before correct diagnosis was made. In a few cases the condition was never properly diagnosed.

The most commonly made erroneous preoperative diagnosis was acute appendicitis, which was incorrectly diagnosed 13 times. Acute cholecystitis, mechanical intestinal obstruction, and acute pancreatitis were other diagnoses made instead of acute perforated ulcer. In 11 other patients an incorrect diagnosis of a miscellaneous group of disorders was made. Errors in diagnosis were most frequently made in elderly female patients. Of 27 females in the seventh and eighth decades of life there were 9 deaths. Failure to make at least a surgical diagnosis in the elderly patient uniformly resulted in a fatality. Errors in the diagnosis of perforated ulcer, although not frequent, are of importance in affecting the rate of mortality.

Some difficulty was encountered in differentiating acute pancreatitis from perforated ulcer. The serum amylase level is usually not elevated in cases of perforated peptic ulcer but it is elevated in enough cases frequently to confuse the diagnosis. In this group of patients with perforations the amylase level was raised to 200 units or more in 16 per cent or 1 of 6 cases. The diagnosis is particularly difficult in the patient with an elevated amylase level who has no free subphrenic air and gives a poor history. To confuse the picture further is the not unlikely possibility of an acute pancreatitis and perforated ulcer occurring together. Many of the patients suffered perforation while on drinking sprees. Two patients in this series had exceedingly high amylase levels preoperatively. One was 7,200 and the other 6,000 Somogyi units. Neither patient had pancreatic disease when the ulcers were closed surgically.

Abdominal tap is of theoretic value inasmuch as the fluid aspirated from the patient with pancreatitis is grossly different from that found spilled through an ulcer perforation. Both fluids, however, are usually alkaline and may give amylase readings of over 80,000 units. Some cases of perforated ulcer with hyperamylasemia have been correctly diagnosed by the use of intragastric contrast media which demonstrated the perforation.

An unusual type of perforation, which is often diagnosed late or not at all is the ulcer in the posterior portion of the duodenum which does not involve the head of the pancreas but perforates freely into the lesser omental bursa. This type was observed in 10 instances in this series. Five of these cases were diagnosed at autopsy.

OPERATIVE TECHNIQUE

Operative technique is only infrequently a factor which affects the mortality rate, but it is an all important one when miscalculations are made. The usual procedure at this hospital has been simple closure of the perforation with interrupted catgut sutures. Whenever possible a tab of omentum has been fixed over the area of closure. No drains are used except occasionally for the incision. This type of operative management has been satisfactory for the majority of patients.

One error in operative management disclosed by this study revolves around inadequate closure of large perforations. Large, late perforations deserve careful attention, for they are the ones which are particularly prone to reperforate with a resultant death or at least a prolonged critical period of illness. The question of draining these large perforations is unsettled. A drain may be of value in alerting the surgeon earlier, if reperforation does occur. Overt reperforation occurred in 15 instances in this group. It requires alert and energetic handling, does not respond well to reclosure, and is probably best managed by fairly early gastric resection.

The surgeon must be alert also to the possibility of simultaneous gastric and duodenal perforations. These occurred in 7 instances in the 15 year survey and were

chiefly noted in debilitated patients. Central nervous system damage predisposes to this type of combined ulcerative process. The surgeon should also recognize at operation the patient in whom a high degree of pyloric obstruction exists. A few patients will have obstruction after simple closure and will require secondary surgical procedures which add to the mortality.

Hemorrhage of any magnitude should also put the surgeon on guard at the time the perforation is closed. A more definitive type of procedure should be considered when bleeding has occurred from a second, nonperforating ("kissing") ulcer, from a large excavative duodenal ulcer, or from a separate gastric ulcer. Simple closure in these instances may invite further trouble. Suture ligatures of the bleeding points are also probably of limited value when nothing is done further to reduce acid secretion. Wedge excision of a bleeding gastric ulcer may suffice for control in the seriously ill patient, but pyloroplasty and vagotomy or resection procedures have recently proved more satisfactory in guarding against further morbidity and mortality in these more complicated and extremely important situations.

Definitive procedures such as subtotal gastrectomy for perforated peptic ulcer merit the increased attention they have received in recent years because of the frequent persistence of severe ulcer disease after perforation. Currently about 25 per cent of our patients are receiving definitive surgical treatment after closure, the majority of these being operated upon within 2 years after perforation. A much larger number, more than 60 per cent, continue to have symptoms after emergency closure of their perforations. When proper preoperative care and selection is practiced, resectional surgery does not appear to increase the mortality associated with acute perforation. This surgical service has recently managed a group of 75 acute perforations with pyloroplasty and vagotomy with but 1 death in the group.

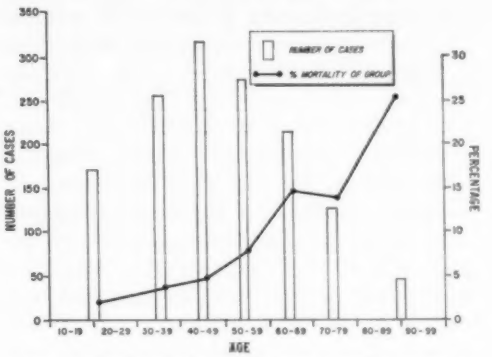


FIG. 2. Deaths resulting from postoperative complications.

POSTOPERATIVE COMPLICATIONS

Because of the frequency of associated diseases and the severe nature of the perforation episode, many complications can occur which affect the final outcome. Complications occurring in the postoperative period are increased in patients who are older and who have multiple diseases. They are fairly common and include intra-abdominal abscesses, duodenal fistula from reperforation, pyloric obstruction, and hemorrhage—all of which are direct complications of the perforated ulcer itself. Other complications occurring in the respiratory and cardiovascular systems are frequent. Subphrenic abscesses may occur and are predominantly right-sided. The incidence of postoperative pneumonitis and shock is also high. In the present group of 1,000 cases, 296 serious complications developed in 202 patients, and in this group there was a 50 per cent mortality. When the incidence of postoperative complications and the mortality are compared by age decades, a rising mortality is noted as the age increases (Fig. 2). Attention to all factors in the preoperative period, wise operative management, and intensive postoperative care will serve to lessen the frequency of complications.

SUMMARY

An appraisal of a large group of patients with perforated gastric and duodenal ulcers

has been presented in order to analyze various factors which separately and in combination affect the mortality rate. The significance of advanced age, the female sex, prolonged duration of the perforation, large perforations, concomitant serious disease in other systems, the incidence of gastric perforations, shock, and erroneous diagnoses have been cited for their particularly adverse effects. The high mortality associated with postoperative complications and concurrent hemorrhage was also noted. Pitfalls in operative management were described.

Tabulated results under each of these categories for 1,000 cases of gastroduodenal perforation occurring on a general surgical service from 1944 through 1958 are used to emphasize the importance of these factors. Suggestions for improvements in both supportive and operative treatment have been made.

REFERENCES

1. Berne, C. J., and Mikkelsen, W. P. Management of perforated peptic ulcer. Surgery, 1958, 44: 591-603.
2. Rogers, F., and Hiatt, N. The natural history of perforated peptic ulcer. Med. Times, Lond., 1959, 87: 367-390.

EDITORIALS

APT WORDS AND TROUBLED MINDS

KENNETH D. DEVINE, M.D., F.A.C.S., Rochester, Minnesota

Apt words have power to suage the tumours of a troubl'd mind. —Milton: *Samson Agonistes.*

THE YOUTHFUL SURGEON, explaining to his patient the particular condition at hand, may use words and phrases which mean much to another surgeon but which only confuse and perhaps frighten the patient. Very likely such an action is only to be expected because for perhaps a decade in the competitive world of the medical school, internship, and residency the young man has been trying to impress others of his kind with his ability to use and understand weighty words and special symbols. Inevitably, except in rare instances, he goes out into the realities of medical practice where he believes he must impress the patient and his family with a conviction of his ability and skill.

Patients of our era have taken on some sophistication in medical matters, and they are no longer impressed by the "treat 'em rough and tell 'em nothing" surgeon. The public expects to ask some questions and deserves to receive some answers when questions of health and medicine are imminent. Now, it is always more impressive when a man possesses the ability to answer questions before they are asked. Explanations and answers given to patients should not be encumbered with words which convey nothing but trouble and foreboding. Simple, everyday phrases and words which at other times or under other circumstances might seem unlettered or rough can elicit a nod or a smile of understanding—a smile of confidence and faith.

Almost anyone who has had the pleasure of reading to children has encountered A. A. Milne's adventures of Winnie-the-Pooh. It was this lovable little creature who said unashamedly, "I am a Bear of Very Little Brain, and long words Bother me." Thus it is, I am sure, with patients not schooled in medicine.

Words such as "windpipe," "voice box," "jawbone," "saliva" or even "spit gland," and "large bowel" are better than "trachea," "larynx," "mandible," "parotid gland," and "colon." Many times I have heard a patient mispronounce the word "biopsy" in such circumstances that I realized that he did not know just what it means. It is better to say that a little piece of flesh, or whatever the tissue in question is, will be removed so that it can be looked at under the microscope by a special doctor who can tell by such an examination what kind of trouble is at hand than it is to say, "We will do a biopsy and have it analyzed by a pathologist."

Instead of saying to the patient, "You have a tumor in your neck which may be serious and you might need a big operation," it is better to say, "There is a lump in your neck and you have come to the doctor to find out what it means. It is as though I had put an orange on the table here and covered it with blankets and asked you to come in and feel through the blan-

kets and tell me exactly what was on the table. You could describe it as being 'round' and 'soft' and 'not attached to the table' and you might guess it to be an orange, tomato or apple. The only way to be certain is to take off the blankets. And so it is with the lump in your neck. I could feel through the skin of your neck and give you a guess, but you don't want a guess; you want to know. So it must be removed and examined with the microscope, and the treatment might require removal of other things in your neck."

I suspect that every successful surgeon, to deal with questions about proposed operations, has developed some favorite phrases, stories, and similes which quickly answer many questions and which satisfy the patient and impart confidence in the surgeon. The sooner the young surgeon develops his own simple way of explaining problems to his patients, the easier his lot will be and the more satisfying his practice will become. The late Gordon B. New in such an incident was a master at what he called "setting the stage." That was his phrase for preparation of the patient and family for the news that an operation was required so that they would have some understanding of what lay ahead. All too often the patient, who has no knowledge of what surgical treatment can and cannot accomplish, expects more from an operation than is reasonable, and for this reason it is better to come to an understanding on this point before and not after the operation.

If the young surgeon, trained to the nth degree, full of confidence and extremely competent, looks about him and is puzzled and perhaps angry at the success of the busy and, to his way of thinking, incompetent or less adequately trained surgeon, he should remember that "there is more to it than just the cutting."

ASCITES, VARICES, OR BOTH?

HAROLD LAUFMAN, M.D., F.A.C.S., Chicago, Illinois

WHY DOES massive ascites alone develop in some patients with hepatic cirrhosis while others escape an ascitic phase and exhibit only esophageal varices and varices of other portal collateral channels, and still others exhibit ascites of varying degrees together with varices?

A corollary question arises from conflicting reports of therapeutic claims for various surgical operations for ascites and varices. If all reports are assumed to be accurate, relief of cirrhotic ascites is obtained with side-to-side portacaval shunt but not with end-to-side shunt; portacaval shunting of any type is considered valuable only for the prevention of recurrent bleeding from esophageal varices but not for the treatment of ascites; end-to-side portacaval shunt relieves both ascites and varices; the double shunt procedure of anastomosing both ends of the portal vein into the vena cava is superior to other methods of shunting; and decompression of the portal system by any surgical method is of little or no value in the treatment of either ascites or varices. Can all these views be reconciled?

It is now generally believed that among other things, hypoproteinemia, sodium retention, and hyperaldosteronism accompanying cirrhotic ascites are perpetuating rather than causative factors. Nonetheless, the initial lesion leading to these and other physiologic aberrations is considered to be the partial obstruction of venous blood flow along its intrahepatic course from the portal to the caval venous systems. Evidence for this view is supplied by animal experiments in which these chemical and hormonal changes in the blood are produced by constricting the thoracic inferior vena cava and are made to disappear by removal of the constriction, or after the development of collateral circulation.

Whether it is associated with ascites or with varices, portal hypertension is spoken of as if it were the result of one pathologic entity. Elevated pressure in the portal vein can usually be demonstrated when either, or both, ascites or varices occur with cirrhosis. But how unequivocal is the evidence that the basic lesion of portal hypertension with ascites is or is not the same as that of portal hypertension with varices?

Ascites of a more or less uniform type has been produced experimentally in the dog, monkey, and other animals by a variety of lesions which block hepatic vein outflow from the liver or which increase caval pressure hydrostatically. The ascites need not necessarily be due directly to the increased portal vein pressure; it may well be a concomitant phenomenon due to lymphatic weeping and plasmapheresis from venous channels under pressure within the liver. Both the transmitted increase in portal vein pressure and the ascites can be considered parallel results of blockage of venous egress from the liver.

Ascites has never been produced experimentally by constriction of the portal vein alone below the liver despite temporary increases in portal pressure which may accrue below such portal vein constrictions. A limited collection of peritoneal fluid results from combined constrictions of the portal vein and inferior vena cava below the diaphragm, but this fluid is not considered true ascitic fluid since it has a lower specific gravity, a lower protein value, and different chemical values than does ascitic fluid. Portal hypertension with varix formation has been produced experimentally by arteriovenous fistulas between the splenic artery and portal vein, but ascites is not a prominent sequel.

Intrahepatic blockades have been accom-

plished in dogs and in rats by injection of foreign material into the portal vein, or into the liver parenchyma, by administration of deficiency diets, hepatotoxic agents, or parasitic infestations. Gastric instillations of carbon tetrachloride have been used to produce cirrhosis in rats. In a large percentage of these cirrhotic rats varices developed and in many some degree of ascites was noted. Some of the animals showed no abnormality in the splenoportogram. These variations are similar to those seen in man and can be ascribed to randomized location and degree of intrahepatic venous blockade resulting from parenchymal cloudy swelling, necrosis, and ensuing cirrhosis.

It has been said that experimental cirrhosis in animals cannot be compared with that occurring in man because species differences in anatomic configurations preclude the production of comparable varices; yet, the ascites can be readily reproduced.

Studies on human cirrhotic livers and on patients with cirrhosis have also led to equivocal data. It was once believed that fibrosis in the cirrhotic liver of man was the main cause of the obstruction. Now the belief is that the random lobulation of the regenerating parenchyma is responsible although fibrosis is known to be present in abundance. It was once believed that the obstruction resided in the terminal radicles of the portal vein. Injection studies of human postmortem livers have demonstrated the blockade to be mainly at the site of the collecting hepatic venules, at least in the specimens examined. Does the new view in each of these considerations supersede the old, or could the pathologic variations of cirrhosis combine both the old and the new observations?

The monkey is the only experimental animal usually able to tolerate sudden complete ligation of the portal vein, as does man. Experiments in which Macaca rhesus monkeys were used have demonstrated that when occlusion of the vena cava and azygos vein was made above the liver the result was ascites, and not esophageal varices, although portal vein pressures remained elevated for about a year. When the constriction was made of the portal vein alone, portal hypertension was transient, and neither ascites nor esophageal varices resulted. If portal vein ligation was followed by the vena cava-azygos ligations, neither ascites nor varices resulted. However, when constriction of hepatic vein outflow was followed by obstruction of the portal vein, ascites was temporary, but esophageal varices developed and remained as the predominant lesion for as long as 5 years.

If the vena cava-azygos ligations above the liver can be likened, in effect, to postsinusoidal obstruction in a cirrhotic liver, then ascites can be expected to be the predominant lesion when the venous obstruction is in the hepatic collecting venules. If the portal vein ligations can be likened to presinusoidal obstruction, both presinusoidal and postsinusoidal obstruction are necessary for the development of varices, provided the postsinusoidal obstruction develops first. The extent to which ascites will develop under these circumstances could depend upon the efficacy of intrahepatic shunting channels and the extent to which hepatic lymphatic and venous channels become dilated. Since in presinusoidal (portal) occlusion the increased pressure is not transmitted through a capillary bed, it can be expected to result in less stasis in hepatic lymphatic and venous channels than does postsinusoidal (hepatic vein) occlusion; therefore, portal vein obstruction is less likely to lead to ascites than is hepatic vein obstruction.

Thus, elevated pressure may be demonstrated in the portal vein with either, or both, presinusoidal or postsinusoidal blockade, but in postsinusoidal blockade the predominating lesion is ascites, whereas in superimposed presinusoidal blockade the varicosities may develop without a phase of massive ascites. When postsinusoidal block becomes extreme enough, varices tend to develop in addition to pre-existing ascites. Any combination of the two underlying

types of intrahepatic blockade is possible, depending on the progression of the lesion and the transmission of the elevated pressure across the sinusoidal vascular bed in either direction.

To the extent that medical measures can counteract the perpetuating factors of ascites or hasten resolution of cloudy swelling of liver cells, they may prevent or lessen ascites and reduce the extent of the intrahepatic venous blockade of either the presinusoidal or postsinusoidal variety. Experimentally produced ascites can be overcome largely by hypophysectomy or bilateral adrenalectomy, both of which deprive an animal of the endocrine perpetuating factors. Not all of these factors are known.

Within the framework of the concept presented, an adequate decompression operation in a postsinusoidal blockade with massive ascites would necessitate leaving continuity in the portal vein as a secondary outflow tract for the alleviation of elevated venous pressure transmitted in a retrograde direction from the hepatic veins to the portal vein. This would favor a side-to-side shunt or a double-barrelled shunt as the most efficacious type of decompression. Medical measures would also be in order to counteract the perpetuating factors. An end-to-side procedure would prove beneficial once varices had developed with or without ascites because collateral outflow channels, the varices, would already be present. The benefit would be derived from the lightened pressure load along these channels which the complete diversion would provide. When infrahepatic or presinusoidal block leads to varices alone, either side-to-side or end-to-side diversion of portal blood should be equally efficacious; reverse portal outflow need not be maintained because varices are already present to serve this purpose.

It is theoretically possible, then, to reconcile conflicting reports of the efficacy of various surgical procedures by employing a concept in which two anatomic types of intrahepatic blockade are assumed to occur in cirrhosis, one presinusoidal, responsible mainly for varices, the other postsinusoidal, responsible mainly for ascites.

That this theory be proved correct is not of great importance. It is offered in the hope of stimulating definitive research to solve the ambivalence and clear away the ambiguities surrounding the pathogenesis and therapy of cirrhosis.

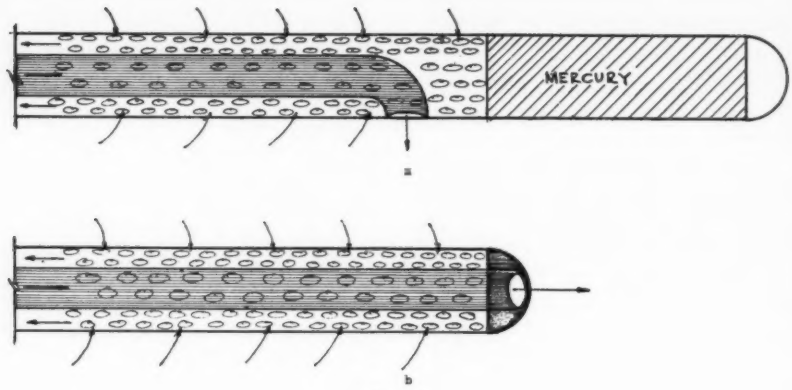


FIG. 1.

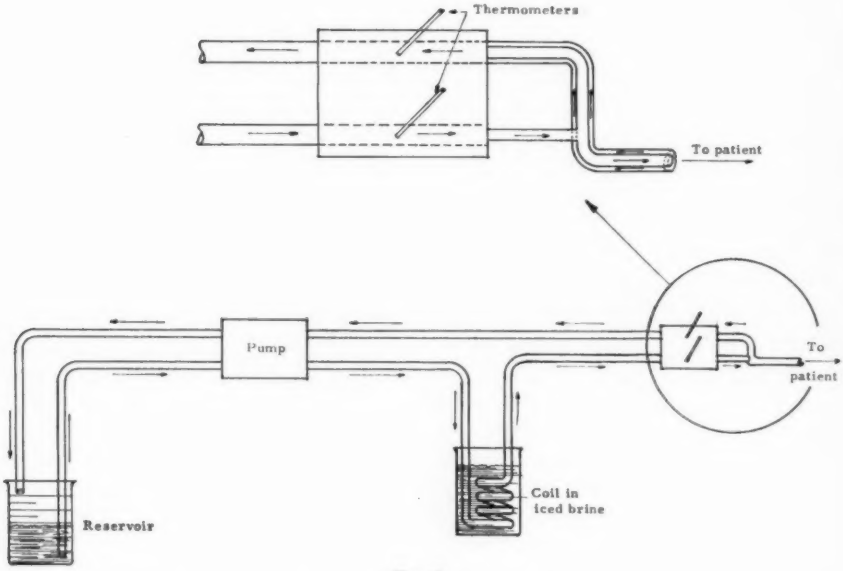


FIG. 2.

FIG. 1. a, Sketch shows tip of a Devine nasogastric tube. b, The mercury tip has been removed and a small plastic tip substituted. This tip has an opening which allows fluid to enter the stomach through the inner lumen of the tube.

FIG. 2. Schematic drawing of the apparatus illustrates the simplicity of construction. The detailed sketch above shows the method of monitoring inflow and outflow temperatures.

Gastric Hypothermia Induced by Gastric Lavage Without a Balloon.—
Jerome L. Sandler, Walter F. Ballinger II, and Joseph L. Medoff.

THE SURGEON AT WORK

GASTRIC HYPOTHERMIA INDUCED BY GASTRIC LAVAGE WITHOUT A BALLOON

JEROME L. SANDLER, M.D., WALTER F. BALLINGER II, M.D., F.A.C.S., and JOSEPH L. MEDOFF, M.D., Philadelphia, Pennsylvania

GASTRIC HYPOTHERMIA has been employed by Wangensteen and others (1) to control upper gastrointestinal hemorrhage from various causes. We prefer continuous gastric lavage without the use of a balloon. For this purpose, a simple device has been constructed. Aside from the pump, all component parts are inexpensive, replaceable and usually may be found in the hospital without purchasing extra equipment. A double lumen Devine nasogastric tube is modified by removing the mercury tip (Fig. 1). The inner lumen carries a buffered solution at 5 degrees C. into the stomach near the pylorus. The lavaging fluid used is that described by Wangensteen and his associates (2); it consists of 5 per cent glucose in water and contains 0.745 gram of potassium chloride and 2 grams of ammonium chloride in each liter, buffered to *p*H 7.4 with sodium bicarbonate. The fluid circulates proximally toward the gastric cardia where it is removed through multiple small openings in the outer lumen of the tube. The fluid leaving the patient averages 15 degrees C. and passes through transparent plastic tubing to a graduated cylinder in which the outflow can be measured. From this container the fluid passes through a sigmamotor pump and then through the coils of copper tubing immersed in a bucket containing crushed ice and salt. The fluid is then returned to the patient. A schematic diagram of the apparatus is shown in Figure 2. The optimal flow rate has been 100 milliliters per minute.

Blood clots have not plugged the tubing. Postlavage serum electrolyte values were not altered. Advantages of direct gastric hypothermia include easier passage of the tube and more rapid and uniform cooling of all portions of the stomach. In addition, cessation of bleeding is evident when clear fluid is returned from the patient after changing to fresh lavaging solution. Loss of fluid from the pylorus has been negligible. Initially, the presence of a gastroenteric anastomosis was considered a contraindication to direct gastric hypothermia because of anticipated fluid loss into the small bowel. Recently, however, this method was used successfully to control bleeding in a patient after gastrojejunostomy. Only 300 milliliters of fluid were lost into the bowel during 4 hours of gastric lavage.

From the Departments of Surgery and Medicine, Jefferson Medical College, Philadelphia.

REFERENCES

1. WANGENSTEEN, O. H., ROOT, H. D., JENSON, C. B., IMAMOGLU, K., and SALMON, P. A. Depression of gastric secretion and digestion by gastric hypothermia; its clinical use in massive hematemesis. Surgery, 1958, 44: 265.
2. WANGENSTEEN, O. H., SALMON, P. A., GRIFFEN, W. O., JR., PATERSON, J. R., and FATTAH, F. Studies of local gastric cooling as related to peptic ulcer. Ann. Surg., 1959, 150: 346.

AN OPERATIVE PROCEDURE FOR CANCER OF THE LIP

ARTHUR L. MURPHY, M.D., F.A.C.S., Halifax, Nova Scotia, Canada

IF ONE-HALF OR MORE of the lower lip is invaded by an epithelioma, clinically, two types of lesions are recognized: (1) a superficial lesion, sometimes multicentric in origin, when the discrete growths may be interspersed with areas of hyperkeratosis; (2) an infiltrating lesion, most often unicentric in origin, which has caused gross destruction of the tissue.

Although excision is the standard treatment for epithelioma of the lip, the broad, superficial lesion is treated by the insertion of radium needles. This method of treatment is preferred to roentgen radiation because it produces less atrophy and less scarring. There has been concern over the theoretic possibility that radium needles might dislodge cancer cells and make them embolic to adjacent lymph nodes. But in the 6 years of existence of the Tumour Clinic, a higher incidence of metastases has not been definitely shown in those cases which were treated by radium implant. This potential embolic hazard can be avoided by the use of a radium mold. Unfortunately, this treatment is more costly, in days and hours, to patient, hospital, and staff.

The destructive lesion is treated by surgical excision, and if more than one-half of the lip is involved then total excision must be carried out.

In earlier years several of the standard flap operations were used for reconstruction of the lower lip after excision. All are rather formidable procedures, and none was found to be satisfactory. A new operation was, therefore, devised. Flaps were taken from the neck because in this area, particularly in the elderly, there is redundant tissue. Good results were obtained from this procedure; but, as with the older methods, great dissection was necessary; muscular control of the lower lip was almost nonexistent, and the late contracture tended to pull down the lip and encourage drooling. Therefore, this procedure was abandoned.

From the Department of Surgery, Victoria General Hospital, and Nova Scotia Tumour Clinic, Halifax, Nova Scotia, Canada.

TECHNIQUE

The operation now in use is a simple, single stage procedure which has proved satisfactory in 9 cases to date. It was developed by combining the original Estlander and Bernard operations (1-3).

The width of the average mouth in repose is 2½ inches. A reduction to 2 inches is accepted as permissible. To replace the lower lip, ¼ inch is taken from the upper lip on one side, (Fig. 1b); ⅜ inch in continuity with this, from the cheek above; and its apposing ⅜ inch from below; this totals 1 inch. A similar procedure performed on the opposite side yields a 2 inch lower lip.

In the first cases, the incision was extended laterally beyond the ⅜ inch mark, and the result was a lower lip which protruded in a full, permanent pout. However, it is better to err with the lower lip oversized than too small since the scar contracture of the 3 vertical incisions will decrease the length of the lip just slightly.

A larger or smaller mouth necessitates a slight adjustment in the measurements.

After the flaps have been sutured into place (Fig. 1d), enough buccal mucosa is dissected free and brought forward to form a new vermilion border.

As in the Estlander operation, the orbicularis oris muscle is turned down to form the new angle of the mouth and the lateral extreme of the lower lip. A portion of the levator anguli oris is taken along with the orbicularis oris and, as the gap above is closed (Fig. 1d), the zygomaticus major is again fixed into place to support the angle. Thus, there is no pulling down of the mouth and no risk of drooling. The 2 central flaps (Fig. 1c) contain fibers of the depressor anguli oris. In this transposed position they are not far from the horizontal and give further muscle stability and control. The mouth will pout on demand.

In most cases, enough fibers of the intraorbital, buccal, and mental nerves escape sectioning so

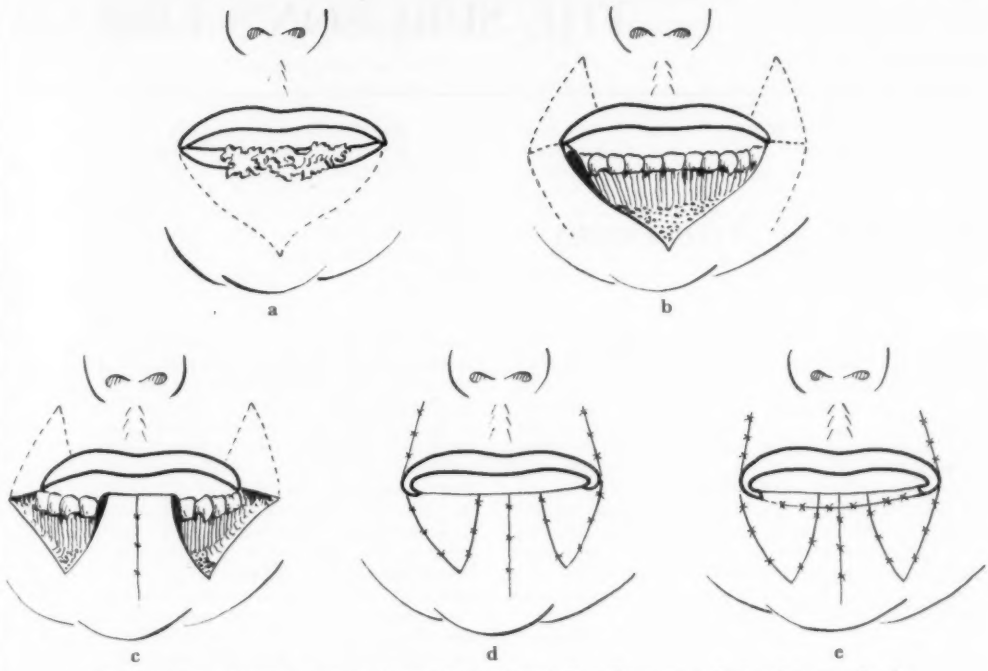


FIG. 1. a, The primary lesion is shown by the dotted line. In a more destructive growth, the excision should be greater inferiorly. b, The base of the superior triangle is ¼ inch long on the lip and ⅜ inch long on the cheek. The inferior flap is ⅜ inch wide. c, The inferior flaps are drawn together in the midline. d, The triangles are swung down from above. e, A new vermilion border is made.

that the patient will have full sensation in the new lip.

Despite the many incisions, there has been no sign of impaired circulation or faulty healing in this series. After healing is firm, stretching of the new lip should be carried out to prevent a contracture which could make the insertion of dentures difficult.

This procedure can readily be combined with radical neck dissection when such operation is indicated.

SUMMARY

An operation is described for replacement of the lower lip after total excision.

REFERENCES

1. BARSKY, A. J. Plastic Surgery. Philadelphia: W. B. Saunders Co., 1938.
2. MARTIN, H. E. Surgery of Head and Neck Tumors. New York: Paul B. Hoeber, Inc., 1957.
3. WARD, G. E., and HENDRICK, J. W. Tumors of the Head and Neck. Baltimore: The Williams & Wilkins Co., 1950.

THE SURGEON'S LIBRARY

Reviews of New Books

HISTORICAL ASPECTS, etiologic mechanisms, blast phenomena, pathologic changes, diagnostic methods, and general principles of treatment pertaining to the subject are included in the small volume entitled *Nonpenetrating Injuries of the Abdomen*.[1] The individual solid and hollow abdominal viscera are then considered separately, and special features of diagnosis and treatment are given for each. In the final chapter, hospital and team organization for the management of trauma, in general, is discussed. The material presented in succinct sentences is factual, authoritative, and current; all aspects of the various facets of the problem are covered. The advocated procedures conform to the best accepted principles.

—*Warner F. Bowers.*

ON FINAL ANALYSIS, the 147 page book *Radiology as a Diagnostic Aid in Clinical Surgery*[2] is more than a manual on radiologic diagnostic procedures, and it is informative in every sense of the word. There can be little doubt that the clinical surgeon is interested in all laboratory procedures which will increase his diagnostic armamentarium and, particularly, in the preoperative and postoperative periods of a given surgical patient.

The important diagnostic aspects so far as x-ray methods are concerned have been excellently summarized in the first 8 chapters. The material in the final chapter is devoted to protective measures for those individuals who use radiologic techniques only occasionally. This relatively short treatise covers radiologic diagnostic principles in the emergency ward; postoperative conditions; the mouth, nose and neck; the alimentary tract; the bilary tract and pancreas; the urinary tract; and bone and vascular investigations. The method used to summarize the various principles and points which the author wanted to make is extremely interesting as, in fact, is the attitude of the essayist when he inferred repeatedly that radiologic diagnostic procedures did not in any way displace the importance of careful clinical observation. Again, the value of the clinical surgeon and the radiologist in combining their efforts to arrive at a correct diagnosis has been re-emphasized. One of the pleas throughout the text is submission of all important clinical details of the surgical patient to the radiologist to help both the surgeon and radiologist arrive at a final accurate diagnosis.

In addition to the 86 excellent reproductions of actual roentgenograms that demonstrate the various points which the author makes throughout the text, one is aware of the various tricks used in his own work to aid diagnostic acumen. For example, in the chapter on the "Alimentary Tract" and, particularly, that portion referring to the diagnosis of polyps of the colon, the author points out his technique in the use of 1½ per cent tannic acid solution in the barium. This method effects good evacuation, collapsing the bowel, and with air insufflation has increased the percentage of positive diagnoses of polyps of the colon. Another example is the technique which he has used to demonstrate lesions of the bladder and posterior urethra. This is an excellent book which combines the points of radiologic diagnosis in association with the problems seen in clinical surgery.

—*Vinton E. Siler.*

OCCASIONALLY a volume appears which puts into words practical suggestions for therapy based upon a rich investigative background. Such a book is *Fluid Balance in Obstetrics*[3] by Philip Rhodes which should be of value to all physicians who include obstetrics in their practice, as well as to obstetric house officers or those responsible for their teaching.

An excellent introduction simplifies a difficult subject, that of physical chemistry related to fluid balance. It gives a workable knowledge even to those many years removed from their preclinical chemistry courses. Physiology of the nonpregnant woman and of the normal pregnant woman provides a background for understanding the abnormal states. Fluid balance and electrolyte problems related to hyperemesis gravidarum, diabetes, toxemias, oliguria, anuria, and hemorrhages are expertly discussed. Finally, the management of those cases most frequently encountered in obstetric practice are summarized in the chapters on normal, prolonged labor and cesarean sections.

Mention is made of considerable investigation, especially in the realm of adrenocorticosteroids. The

[1] NONPENETRATING INJURIES OF THE ABDOMEN. By Robert H. Kennedy, B.A., M.D., F.A.C.S. 120 pages. $4.75. Springfield, Ill.: Charles C Thomas, 1960.

[2] RADIOLOGY AS A DIAGNOSTIC AID IN CLINICAL SURGERY. By Howard Middlemiss, M.D., F.F.R., D.M.R.D. 151 pages, illustrated. $7.50. Springfield, Ill.: Charles C Thomas, 1960.

[3] FLUID BALANCE IN OBSTETRICS; A CRITICAL REVIEW. By Philip Rhodes, M.A., M.B., F.R.C.S. (Eng.), M.R.C.O.G. 169 pages. $5.75. Chicago: The Year Book Publishers, Inc., 1960.

references after each chapter will aid those who desire further details.

This volume is a scholarly, concise, and well written reference. —*Charlotte H. Kerr.*

A DETAILED ACCOUNT of the bronchovascular structures of the lungs as determined by the study of plastic casts of these structures is presented in *Surgical Anatomy of the Bronchovascular Segments.*[4] Beautiful photographic reproductions of many of the casts and black and white line drawings of portions of these illustrate more clearly the important features of the demonstrated relationships. The use of color, red for arterial structures and green for venous structures, in some of these drawings lends additional clarity to aid in the spatial relationships.

Not only are the standard patterns demonstrated, but also the variations encountered in the study are shown. In addition, the frequency of these is noted, and ready reference is supplied by the 63 tables in the text. Unfortunately, some of the value of these is lost by the use of "formula-writing" for the different types of branching of the structures. It is granted that such a method of designation as introduced by Boyden and co-workers is necessary for comparative studies and for detailed anatomic reference. Yet, for practical use, such terminology rapidly becomes confusing even to those who are familiar with the structures under consideration.

The sections on surgical consideration of the lobes and their individual segments are excellent, and points regarding the normal anatomic features as well as the variations are discussed. These should be of practical value to anyone engaged in this type of surgery. The employment of resection of the individual segments of the middle lobe and of the separate basal segments of the lower lobe is infrequently required except under unusual circumstances, but the admonishment of the necessity of preservation of the venous pattern of the retained segment or segments is well taken, for herein lies the success of such a procedure.

The chapter on the roentgenographic demonstration of the bronchial and vascular anatomy is an extra dividend and adds further to the value of this text. The volume is highly recommended for the anatomist, roentgenologist, pathologist, and surgeon who are engaged in the treatment of diseases of the lung.

—*Thomas W. Shields.*

IN THE SECOND EDITION of a *Manual of Hand Injuries,*[5] the author has revised and added material which includes a chapter on crush injuries. Although the book is concerned principally with the management of acute injuries, the last 2 chapters are devoted to secondary reconstructive procedures. There is no bibliography; however, the author frequently quotes other writers in the text and in footnotes. This manual can be recommended highly to surgeons and surgical trainees.

The book has been expanded by an additional 20 illustrations and 48 pages, although the organization of the book remains the same. Surgical anatomy of the hand and forearm is covered concisely in the first chapter which contains 7 color plates. As before, the anatomic drawings lack something both in detail and depth even though color has been added.

In the second chapter on general technique, local and regional anesthesia are discussed. Line drawings are used to demonstrate the sites of injection of the anesthetic agent. A photograph of gangrene of a finger serves to warn the reader of the potential danger of digital nerve block within the finger.

The chapter on burns includes thermal, mangle, friction, electric, and radiation injuries of the hand. There is a concise presentation on burn shock which is, however, encountered rarely when only the hands are burned.

Skin grafting techniques are adequately covered in Chapter VI. The use of pedicled flaps is discussed in Chapter VII and includes new material on the cross finger flap. A new chapter on crush injuries is accompanied by illustrations and photographs of several complex, mutilating injuries. Acute tendon and nerve injuries are presented thoroughly in the next 2 chapters.

Bone and joint injuries of the lower forearm and wrist are included in the chapter on fractures and dislocations which is comprehensive and practical. The coverage of infections is also concise and adequate. A section on secondary tendon repairs and tendon grafting is prefaced by the warning that these elective procedures should be undertaken only by the experienced surgeon. In the last chapter, degenerative diseases of peritendinous tissues are presented along with a brief section on bone grafting, Z-plasty, and other specialized procedures. —*John L. Bell.*

EXPERIENCES with more than 6,000 cases at the Memorial Hospital in New York City comprise the volume *Tumors of Childhood.*[6] Dargeon has intended this work mainly for the clinician, so that details of surgical management and discussion of fine points in pathologic variants are usually omitted.

The book begins with a section including historical references, etiologic agents, and a detailed analysis of the incidence of various tumors in children. The next portion deals with multiple aspects of diagnosis and therapy. Much attention is given to chemotherapy and radiotherapy. In the remainder of the treatise there is an orderly and detailed discussion of every tumor which occurs in childhood. Some mention is even made of nonneoplastic tumors, such as omphalocele and trichophytobezoar in differential diagnosis. Charts showing the details of the cases observed by the author are included with each of the commoner tumor types. A majority of the many well produced illustrations are of patients, roentgenograms, and gross pathologic specimens. Relatively few microscopic sections have been included.

[4] SURGICAL ANATOMY OF THE BRONCHOVASCULAR SEGMENTS. By William E. Bloomer, M.D., Averill A. Liebow, M.D., and Milton R. Hales, M.D. With a foreword by Gustaf E. Lindskog, M.D. 273 pages, 208 illustrations. $16.50. Springfield, Ill.: Charles C Thomas, 1960.

[5] MANUAL OF HAND INJURIES. By H. Minor Nichols, M.D. 2nd ed. Foreword by Michael L. Mason, M.D. 400 pages, illustrated. $11.00. Chicago: The Year Book Publishers, Inc., 1960.

[6] TUMORS OF CHILDHOOD. By Harold W. Dargeon, M.D. 476 pages, 315 illustrations. $20.00. New York: Paul B. Hoeber, Inc., 1960.

Understandably, most attention is given to the more common or perplexing problems. Large sections are devoted to malignant diseases of the hematopoietic system, bone tumors, and neurogenic tumors. One chapter is devoted to reticuloendotheliosis. Large biographies are given for each subject.

The volume is well bound and easily read. The reproductions are excellent. It should be of value and interest especially to pediatricians, pathologists, and all those who are either interested in or concerned with the problems of neoplasms in children.

—*William L. Riker.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Carcinoma in Situ of the Uterine Cervix. By Gilbert H. Friedell, M.D., Arthur T. Hertig, M.D., and Paul A. Younge, M.D. 139 pages, 98 illustrations. $7.50. Springfield, Ill.: Charles C Thomas, 1960.

Progress in Experimental Tumor Research. Edited by F. Homburger. 476 pages, illustrated. $22.00. Philadelphia and Montreal: J. B. Lippincott Co., 1960.

Electrical Studies on the Unanesthetized Brain. Edited by Estelle R. Ramey, Ph.D., and Desmond S. O'Doherty, M.D. A Symposium with 49 Participants. 423 pages, illustrated. $6.00. New York: Paul B. Hoeber, Inc., Medical Division of Harper & Bros., 1960.

Treatment of Cancer and Allied Diseases. 2nd ed. Vol. IV—Tumors of the Breast, Chest, and Esophagus. By 67 authors. Edited by George T. Pack, M.D., F.A.C.S., and Irving M. Ariel, M.D., F.A.C.S. 667 pages, 650 illustrations. $30.00. New York: Paul B. Hoeber, Inc., Medical Division of Harper & Bros., 1960.

Cirrhosis of the Liver. By Martin Seler Kleckner, Jr., A.B., M.S. in Internal Medicine, M.D. Forewords by J. Arnold Bargen, M.D., and Archie H. Baggenstoss, M.D. 729 pages, illustrated. $24.50. Springfield, Ill.: Charles C Thomas, 1960.

Medical and Biological Research in Israel. Edited by Moshe Prywes. 562 pages, illustrated. $8.00. Jerusalem, Israel: The Hebrew University of Jerusalem; Hadassah, The Women's Zionist Organization of America, 1960; obtainable through Grune & Stratton, Inc., New York.

Over de Behandeling; van zwangeren met een gestoorde bloedsuikercurve en de resultaten ten aanzien van de fetal loss. By Roger Omers. 128 pages, illustrated. Heerlen, Netherland: N. V. Uitgeverij Winants, 1960.

Occupational Diseases and Industrial Medicine. By Rutherford T. Johnstone, M.D., and Seward E. Miller, M.D. 482 pages, illustrated. $12.00. Philadelphia: W. B. Saunders Co., 1960.

Rypins' Medical Licensure Examinations. Edited by Walter L. Biering, M.D. 805 pages. $11.00. Philadelphia: J. B. Lippincott Co., 1960.

A Practice of General Anaesthesia for Neurosurgery. By Robert I. W. Ballantine, M.R.C.S., L.R.C.P., D.A., F.F.A.R.C.S. With the collaboration of Ian Jackson, M.R.C.S., L.R.C.P., D.A. Foreword by J. E. A. O'Connell, M.S., F.R.C.S. 152 pages, 68 illustrations. $6.50. Boston: Little, Brown & Co., 1960.

Fundamentals of Chest Roentgenology. By Benjamin Felson, M.D. 301 pages, 450 illustrations. $10.00. Philadelphia and London: W. B. Saunders Co., 1960.

Atlas of Clinical Hematology. By Katsuji Kato, Ph.D., M.D. 296 pages, 92 illustrations in color. $25.00. New York and London: Grune & Stratton, 1960.

Il grande omento: patologia e clinica. By Guido de Rosa. Padova, Italy: Tipografia del Seminario di Padova, 1959.

Modern Medical Monographs. Edited by Irving S. Wright, M.D., and Richard H. Orr, M.D. Pseudomonas Aeruginosa Infections. By Claude E. Forkner, Jr., M.D. 104 pages, illustrated. $5.25. New York and London: Grune & Stratton, 1960.

The Management of Fractures and Soft Tissue Injuries. By the Committee on Trauma, American College of Surgeons. 372 pages, illustrated. $5.00. Philadelphia and London: W. B. Saunders Co., 1960.

Correspondence

SOME HEMODYNAMIC EFFECTS OF UREA—*A Correction.*

In Figure 4 of the article entitled "Some Hemodynamic Effects of Urea" by Gustavo Bounous, Mario Onnis, and Harris B Shumacker, Jr., which appeared in the September 1960 issue on page 309, superior vena caval flow was erroneously labeled inferior vena caval flow and vice versa by the authors.

DOES NOT CIRCULATE

THE UNIVERSITY OF MICHIGAN
DEC 5 1960
MEDICAL LIBRARY

SURGERY
Gynecology & Obstetrics

WITH

INTERNATIONAL ABSTRACTS OF SURGERY

December, 1960

VOLUME 111 · NUMBER 6

PLASMANATE®

HUMAN PLASMA PROTEIN SOLUTION

"...the agent of choice in the initial treatment of shock..."[1]

increases circulating blood volume with outstanding effectiveness . . . unsurpassed safety

Clinical demonstrations have borne out the usefulness and safety of Plasmanate.[2] It offers all the advantages of plasma with none of its undesirable properties and it has a better balanced electrolyte content than albumin. Its plasma expanding properties have been shown to be equivalent to those of an equal amount of protein in the form of human serum albumin.[2] Unlike whole blood, it does not alter the blood typing characteristics of the recipient, nor does it appear to sensitize patients to its subsequent administration. Plasmanate offers these other advantages:

Heat-treated for 10 hours at 60° C. against hepatitis virus● As reaction-free as normal serum albumin ● Maintains increased blood volume for a reasonable time ● Valuable as a source of protein in treating hypoproteinemia ● Virtually potassium-free and low in Na and Ca ● Can be stored for long periods with no clumping or precipitation.

A New Human Blood Fraction Product from Cutter Research

Plasmanate, a 5% solution of selected human plasma proteins with stabilizers in 0.67% saline solution (pH 6.75-7.25),* is available in 250 cc. bottles complete with ready-to-use administration set.

Electrolytes per liter		Plasma protein percentages	
Sodium	112 mEq.	Albumin	88%
Chloride	48 mEq.	Alpha-globulin	7%
Potassium	0.5 mEq.	Beta-globulin	5%

*U.S.A. and Foreign Pat. Pend.

1. Cock, T. C., *et al.*: California Med. *89*:257, 1958.
2. Bertrand, J. J., *et al.*: Vox Sanguinis *4*:385, 1959.

CUTTER LABORATORIES Berkeley, California

For complete information See PDR page 665

Ask Your Cutter Man or write to Dept. O-17M

labor pain

almost immediate relief for the mother[1]

Satisfactory relief of labor pain was reported by 123 of 147 patients given LERITINE. Most patients promptly went to sleep...were easily aroused... rested quietly between pains. Respiratory depression or hypotension was not observed. Nausea and vomiting were rare. Length of labor was not affected.[1]

Barbiturates were unnecessary in most patients. When used, they were effective in half the usual amount.[1]

Parenteral use in obstetrics: 50 mg. of LERITINE (2½ times more potent than meperidine), given intramuscularly or subcutaneously and repeated, if necessary, in three or four hours for a total dose of 100 to 200 mg. For rapid action: 10 mg. in dilution intravenously, by slow injection, simultaneously with 40 mg. intramuscularly or subcutaneously.

minimal sedation, reduced hazards for the infant[1]

Infants were given high Apgar ratings on respiratory effort, heart rate, muscle tone, reflex irritability, and color. Only one needed NALLINE* (nalorphine) to counteract respiratory depression.[1]

Precautions: Respiratory depression due to LERITINE may rarely occur. If it should, it may be reversed by the antagonist NALLINE, thus providing an additional margin of safety. (Consult package circular for comprehensive statement on all precautions.)

Warning: May be habit-forming. Notice: Subject to the Federal Narcotic Law.

Additional information on LERITINE and NALLINE is available to physicians on request.

*LERITINE and NALLINE are trademarks of Merck & Co., Inc.

1. Wizenberg, M. J., et al.: Am. J. Obst. & Gynec. 78:405 (Aug.) 1959

Leritine*

anileridine

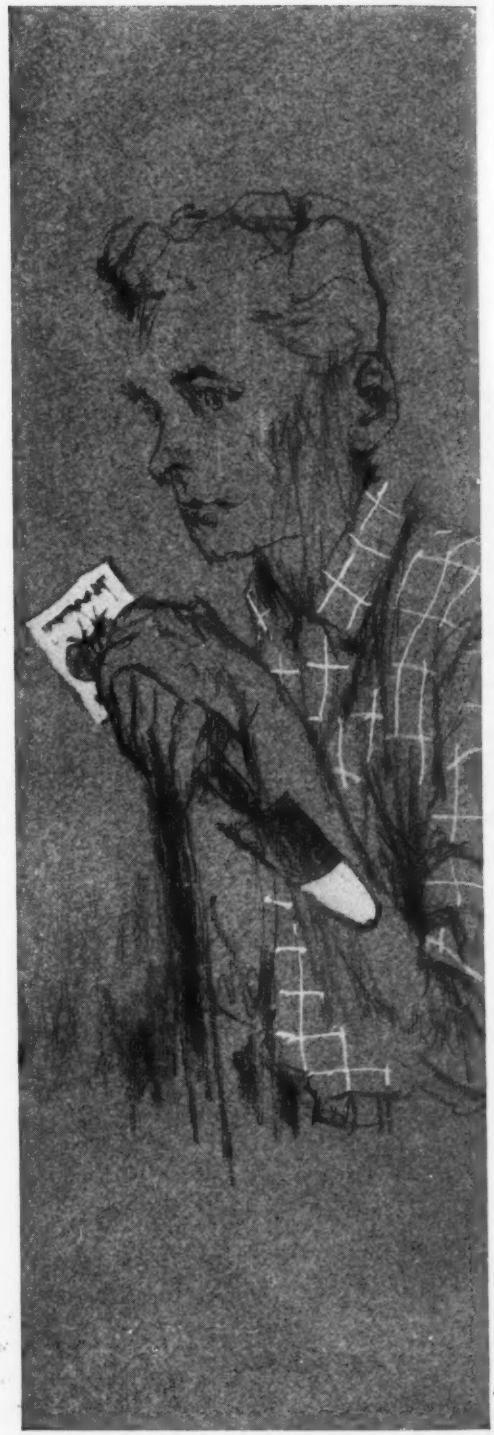
EVEN FOR INTENSE PAIN

MSD MERCK SHARP & DOHME
Division of Merck & Co., Inc. • West Point, Pa.

In Underweight, Malnourished Patients

NILEVAR®

Provides Lasting, Substantial Gains in Weight



NILEVAR has been established as a valuable agent[1] for producing gain in weight and increases in appetite, muscle mass and strength in patients with such specific debilitating injuries and diseases as diabetes mellitus, hip fracture, osteomyelitis, osteoporosis, ileitis and rheumatoid arthritis.

Investigators have found its proved anabolic activity to be highly useful also in the more general problem of malnourished underweight patients. Weight gain in individual patients has been described as dramatic.

Kory and his associates[2] assessed the protein-building effects of Nilevar in fifty-six underweight adults. "Statistically significant gains in weight were observed in all groups receiving norethandrolone [Nilevar]...these usually were accompanied by increases in appetite and sense of well-being. The average weight gain was two pounds per month. The maximum was 20 pounds in six months. No patient exhibited edema or other signs of fluid retention."

Since lean tissue is added, patients who gain weight on Nilevar therapy typically retain it.

The suggested daily oral dosage for adults is 30 mg. of Nilevar for one to two weeks. Subsequently, depending on the response of the patient, this dosage may be reduced to 10 or 20 mg. daily. Continuous courses of therapy should not exceed three months, but may be repeated after rest periods of one month.

Nilevar (brand of norethandrolone) is supplied as tablets of 10 mg., drops of 0.25 mg. per drop and ampuls of 25 mg. in 1 cc. of sesame oil with benzyl alcohol.

1. Carter, A. C.; Weisenfeld, S., and Goldner, M. G., Proc. Soc. Exper. Biol. & Med. 98:593 (July) 1958. 2. Kory, R. C.; Watson, R. N.; Bradley, M. H., and Peters, B. J., J. Clin. Invest, 36:907 (June, part 1) 1957.

G. D. SEARLE & CO.
CHICAGO 80, ILLINOIS

Research in the Service of Medicine

SURGERY

Gynecology & Obstetrics DECEMBER 1960

With International Abstracts of Surgery

OFFICIAL SCIENTIFIC JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS

Editor, LOYAL DAVIS

Associate Editors

WALTER W. CARROLL · F. JOHN LEWIS
MICHAEL L. MASON · JAMES T. PRIESTLEY

UNITED STATES AND CANADA
BRIAN BLADES · JOHN C. BURCH
FREDERICK W. COOPER, JR. · OSCAR CREECH, JR.
WILLIAM P. LONGMIRE, JR. · IAN MACDONALD
ANGUS D. McLACHLIN · S. W. MOORE
HAROLD A. SOFIELD · JAMES C. WHITE

GREAT BRITAIN
IAN AIRD · HEDLEY ATKINS
JOHN BRUCE · W. ARTHUR MACKEY
SIR JAMES PATERSON ROSS

ARGENTINA CARLOS A. TANTURI
AUSTRALIA KENNETH W. STARR
DENMARK E. DAHL-IVERSEN
FRANCE RENÉ FONTAINE
ITALY PIETRO VALDONI
NORWAY CARL SEMB
SWEDEN PHILIP SANDBLOM
URUGUAY PEDRO LARGHERO YBARZ

Published by

THE FRANKLIN H. MARTIN MEMORIAL FOUNDATION
JAMES S. SHANNON, *General Manager*

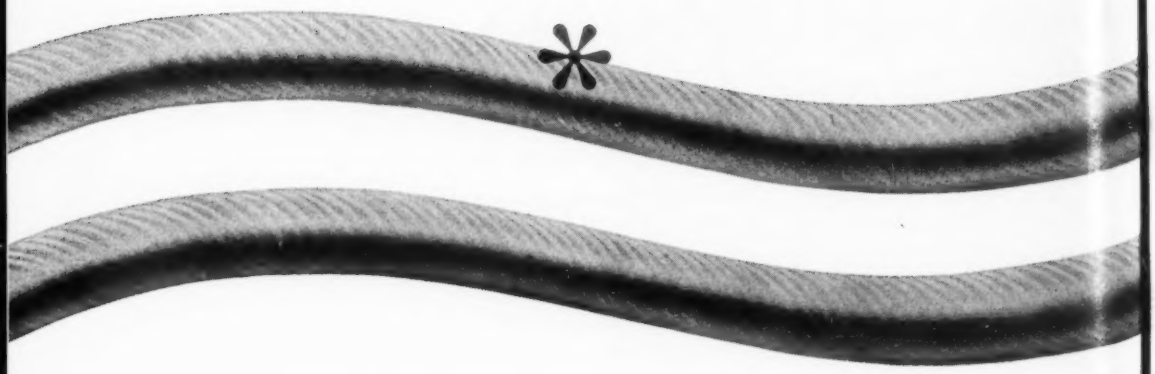
EDITORIAL AND BUSINESS OFFICES · 54 EAST ERIE STREET, CHICAGO 11, ILLINOIS, U. S. A.

Annual Subscription: United States and Canada, $15.00; Other Countries, $17.00. Published Monthly. Entered as second-class matter January 14, 1931, at the postoffice at Chicago, Ill., under the Act of Congress, March 3, 1879.

Copyright, 1960, by The Franklin H. Martin Memorial Foundation.

London Office: 8 Henrietta Street, Covent Garden, W. C. 2.

they may look the same...but



one suture is collagen-pure

Because ETHICON Surgical Gut is Collagen-Pure, it is virtually non-antigenic... causes minimal tissue reaction. And the strength and pliability inherent in Collagen-Pure Sutures are preserved by Electron Beam Sterilization.

* collagen-pure surgical gut

electron beam sterilized

ETHICON®

SURGERY
Gynecology & Obstetrics

DECEMBER 1960

VOLUME 111
NUMBER 6

CONTENTS

THE FATE OF HOMOGRAFTS AND PROSTHESES OF THE HUMAN AORTA. *Béla Halpert, M.D., F.C.A.P., Michael E. DeBakey, M.D., F.A.C.S., George L. Jordan, Jr., M.D., F.A.C.S.,* and *Walter S. Henly, M.D.*, Houston, Texas 659

A CLINICAL STUDY OF CIRCULATING TUMOR CELLS IN MALIGNANT MELANOMA. *Marvin M. Romsdahl, M.D.*, Chicago, Illinois, *John F. Potter, M.D.*, Washington, District of Columbia, *Richard A. Malmgren, M.D., Elizabeth W. Chu, M.D., Clyde O. Brindley, M.D.*, and *Robert R. Smith, M.D.*, Bethesda, Maryland 675

THE ABOLITION OF RENAL AUTOREGULATION BY RENAL DECAPSULATION. *Gustavo Bounous, M.D., Mario Onnis, M.D.*, and *Harris B Shumacker, Jr., M.D., F.A.C.S.*, Indianapolis, Indiana 682

AN ANALYSIS OF THE ROLE OF RADICAL SURGERY FOR GASTRIC CANCER. *Walter Lawrence, Jr., M.D., F.A.C.S.*, and *Gordon McNeer, M.D., F.A.C.S.*, New York, New York 691

OBSERVATIONS ON THE ROLE OF THE LIVER IN HYDROCORTISONE METABOLISM. *Richard W. Steenburg, M.D., Louis L. Smith, M.D., William C. Shoemaker, M.D.*, and *Francis D. Moore, M.D., F.A.C.S.*, Boston, Massachusetts 697

SURGICAL ANATOMY OF THE INGUINAL REGION BASED UPON A STUDY OF 500 BODY-HALVES. *Barry J. Anson, Ph.D. (Med.Sc.)*, Chicago, Illinois, *Edward H. Morgan, M.D.*, Seattle, Washington, and *Chester B. McVay, M.D., F.A.C.S.*, Yankton, South Dakota 707

COMPLICATIONS OF COLOTOMY AND POLYPECTOMY. *George Kleinfeld, M.D.*, and *Frank E. Gump, M.D.*, New York, New York 726

USE OF PACKED RED CELLS VERSUS WHOLE BLOOD IN THE PRESENCE OF IMPAIRED CARDIAC RESERVE. *Martin L. Dalton, Jr., M.D., Henry Tyler, B.S.*, and *James D. Hardy, M.D., F.A.C.S.*, Jackson, Mississippi 729

[CONTENTS CONTINUED ON PAGE 7]

AFTER SURGERY OR DELIVERY . . .

COZYME®

(*d*-pantothenyl alcohol, Travenol)

TO PREVENT AND CORRECT ABDOMINAL DISTENTION

• enables peristalsis to resume within 24-48 hours • complete absence of side effects • reduced use of enemas • lessened incidence of urinary retention.

Now available in new single dose, 2 ml. disposable sterile, nonpyrogenic syringe for greater convenience in administration. Packaged with sterile needle as single unit. Each 2 ml. syringe contains 250 mg. per ml. of *d*-pantothenyl alcohol.

Also supplied in 10 ml. multiple dose and 2 ml. single dose vial, each containing 250 mg. per ml. of *d*-pantothenyl alcohol.

TRAVENOL LABORATORIES, INC. • Morton Grove, Illinois
Pharmaceutical Products Division of **BAXTER LABORATORIES, INC.**

Reconstructive Problems in Canine Liver Homotransplantation with Special Reference to the Postoperative Role of Hepatic Venous Flow. *T. E. Starzl, M.D., Ph.D., Harry A. Kaupp, Jr., M.D., Donald R. Brock, M.D., Robert E. Lazarus, B.A.*, and *Robert V. Johnson, M.D.*, Chicago, Illinois 733

Intermittent Cold Coronary Perfusion as an Adjunct to Open Heart Surgery. *William F. Bernhard, M.D., Hans F. Schwarz, M.D.*, and *Netar P. Mallick, B.Sc., M.B., Ch.B.*, Boston, Massachusetts 744

Acute Necrotizing Colitis Proximal to Obstructing Neoplasms of the Colon. *Alfred Hurwitz, M.D., F.A.C.S.*, and *Rene A. Khafif, M.D.*, Brooklyn, New York .. 749

A Roentgenographic and Clinical Study of the Larynx and Pharynx. *R. Sheehan, M.D., F. Lessmann, M.D., F. Marchetta, M.D., F.A.C.S.*, and *R. K. Lin, M.D.*, Buffalo, New York 753

Scirrhous Carcinoma of the Colon and Rectum. *James C. Fahl, M.D., F.A.C.S., Malcolm B. Dockerty, M.D.*, and *Edward S. Judd, M.D., F.A.C.S.*, Rochester, Minnesota 759

Fibrosarcoma of the Thyroid Gland. *V. E. Chesky, M.D., F.A.C.S., C. A. Hellwig, M.D., F.C.A.P.*, and *J. W. Welch, M.D.*, Halstead, Kansas 767

Factors Affecting the Mortality from Acute Gastroduodenal Perforation. *Frank A. Rogers, M.D., F.A.C.S.*, Whittier, California 771

EDITORIALS

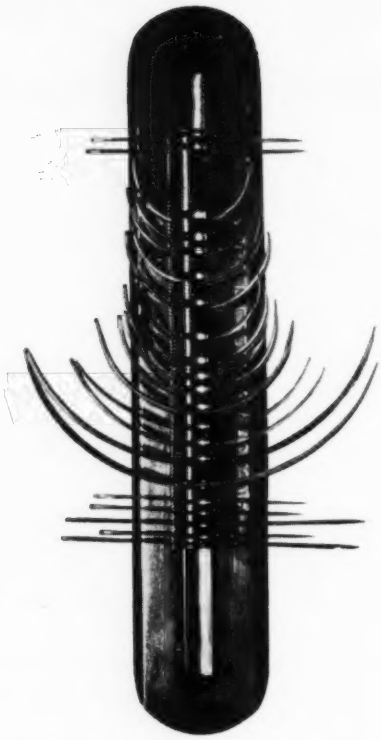
Apt Words and Troubled Minds. *Kenneth D. Devine, M.D., F.A.C.S.*, Rochester, Minnesota 779

Ascites, Varices, or Both? *Harold Laufman, M.D., F.A.C.S.*, Chicago, Illinois 781

THE SURGEON AT WORK

Gastric Hypothermia Induced by Gastric Lavage Without a Balloon. *Jerome L. Sandler, M.D., Walter F. Ballinger II, M.D., F.A.C.S.*, and *Joseph L. Medoff, M.D.*, Philadelphia, Pennsylvania 784

[Contents Continued on Page 9]



Before surgery

you can control apprehension, agitation and tension without depressing respiratory or circulatory functions[2,1]

NEW LIBRIUM

Onset of Librium effect is rapid — often seen within 15 to 30 minutes.[2-4]

Scope of activity — Librium covers the entire clinical range of meprobamate[5,6] and "equanimity-producing" drugs plus a significant portion of phenothiazine indications[6] plus the difficult middle ground between the two.[5]

Record of safety — Librium lacks autonomic blocking and extrapyramidal effects;[7] it is devoid of the potential toxicity of the phenothiazines;[5] not encumbered by the depressions that may follow reserpine.[6]

Reports on Librium: 1. N. Toll, **Dis. Nerv. System, 21**:264, 1960. **2.** H. A. Bowes, **Dis. Nerv. System, 21**:(Suppl.), 20, 1960. **3.** G. L. Usdin, **J. Louisiana M. Soc., 112**:142, 1960. **4.** I. N. Rosenstein and C. W. Silverblatt, paper read at Pan American Medical Association, 35th Anniversary Congress, Mexico City, Mexico, May 2-11, 1960. **5.** I. M. Cohen, Discussant, **Dis. Nerv. System, 21**:(Suppl.), 35, 1960. **6.** G. A. Constant, **ibid.**, p. 37. **7.** T. H. Harris, **J.A.M.A., 172**:1162, 1960.

Consult literature and dosage information, available on request, before prescribing.

ROCHE
LABORATORIES

THE SURGEON AT WORK—Continued

AN OPERATIVE PROCEDURE FOR CANCER OF THE LIP. *Arthur L. Murphy, M.D., F.A.C.S.*, Halifax, Nova Scotia, Canada 786

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS 788–790

BOOKS RECEIVED 790

CORRESPONDENCE

SOME HEMODYNAMIC EFFECTS OF UREA—*A Correction* 790

INDEX TO VOLUME 111

CONTRIBUTORS, SUBJECT MATTER, BOOK REVIEWS ..... i–xii

International Abstracts of Surgery

COLLECTIVE REVIEW

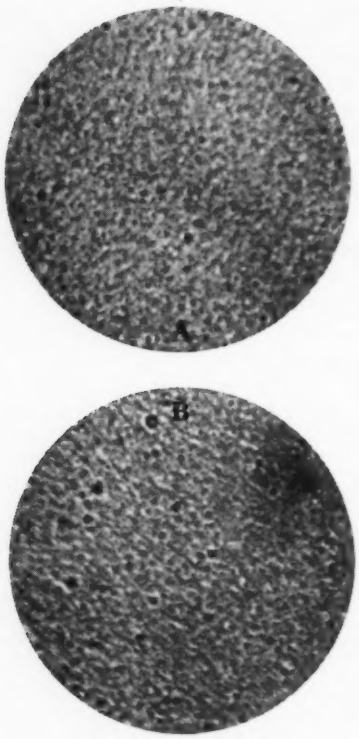
SOFT TISSUE INJURIES OF THE CERVICAL REGION. *Charles A. Hubay, M.D., F.A.C.S.*, Cleveland, Ohio 511–522

ABSTRACTS OF CURRENT LITERATURE

CONTENTS [*following page 522*] ..... iii–viii

ABSTRACTS OF IMPORTANT ARTICLES 523–574

INDEX—ABSTRACTS, VOLUME 111, SUBJECT MATTER, AUTHORS ..... i–xl



Which is chyle and which is Lipomul I.V.?†

As you know, after digestion, fat passes as an emulsion called chyle through the lacteals into the lymphatics tributary to the thoracic duct, and then into the systemic circulation. Lipomul I.V., like chyle, is a *fine milk-white emulsion of fat.* Its fat particles approximate those of chyle in size: about *1/7 the diameter of the normal red blood cell.* Because of this minute particle size, like chyle, Lipomul I.V. is *non-irritating to the vein.* The fat provides *8 times more protein-sparing calories* per cc. than does 5% glucose. It is *swiftly* and *completely metabolized.* **Therefore,** when formation of chyle, a major source of calories, is blocked during pre- and post-operative "digestive tract bypass", many surgeons add Lipomul I.V. to their standard fluid and electrolyte regimen to provide the most concentrated source of energy.

†**A**—Mammalian chyle (magnified 2500X)
B—Lipomul I.V. (magnified 2500X)

Formula:

Cottonseed Oil	15% w/v
Dextrose Anhydrous	4% w/v
Lecithin	1.2% w/v
Oxyethylene oxypropylene polymer	0.3% w/v

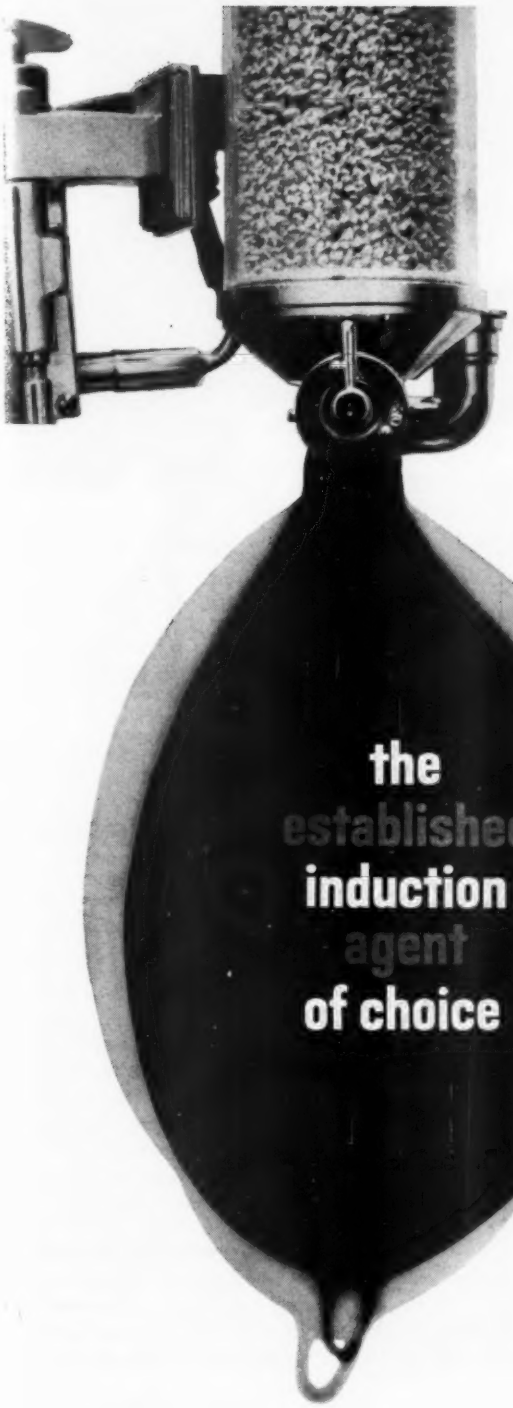
Supplied in 250 cc. and 500 cc. bottles

Lipomul I.V.

Trademark, Reg. U. S. Pat. Off.

Upjohn

The Upjohn Company, Kalamazoo, Michigan



"Induction of anesthesia with . . . vinyl ether is smoother and more rapid than with ether, chloroform, or nitrous oxide. Unconsciousness occurs in one-half to one minute and muscular relaxation in two to three minutes. The incidence of excitement is low, and struggle rarely occurs. Induction is so rapid that analgesia without unconsciousness is seldom observed. Laryngeal irritation or spasm is infrequent. . . .

"Muscular relaxation is approximately as complete with vinyl ether as with ethyl ether. . . .

"Recovery from vinyl ether anesthesia is rapid, smooth, and usually free from emergence excitement. . . . The incidence of vomiting is exceptionally low, being about 2 per cent. Respiratory complications are rare . . . few postoperative pulmonary sequelae."*

VINETHENE®

(VINYL ETHER FOR ANESTHESIA, U.S.P.)

Supplied: In 10-cc., 25-cc., 50-cc., and 75-cc. bottles, each with adjustable plastic dropper cap.

*Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, The Macmillan Company, 1955, p. 66.

VINETHENE is a trademark of Merck & Co., INC.

MSD

MERCK SHARP & DOHME
Division of Merck & Co., INC.
West Point, Pa.

AFTER THE BLESSED EVENT

DERMOPLAST® AEROSOL

SOOTHING TOPICAL ANESTHETIC • BACTERICIDAL • FUNGICIDAL SPRAY

APPLIED WITHOUT TOUCHING THE INVOLVED SENSITIVE AREAS—*Immediate relief of pain and itching is experienced.*

Formula: benzocaine 4.5%, benzethonium chloride 0.1%; menthol 0.5%; dissolved in oils (DOHO PROCESS)

Available in 3 sizes:

PRESCRIPTION: new 3 oz.
(for individual therapy in hospital & home)
HOSPITAL: 12 oz. economy
JUNIOR: 6 oz.

Other indications responding to DERMOPLAST's quick, therapeutic pain relief:

perineal suturing
hemorrhoids
pruritus vulvae
wounds
burns
abrasions
sunburn

Supporting clinical data on request

MALLON DIVISION OF **DOHO**
100 VARICK ST., NEW YORK 13, N. Y.

PMB 400

"PREMARIN"® WITH MEPROBAMATE

FOR PROVEN MENOPAUSAL BENEFITS

The vast majority of menopausal women, especially on the first visit, are nervous, apprehensive, and tense. PMB-200 or PMB-400 gives your patient the advantage of **extra** relief from anxiety and tension, particularly when the patient is "high strung," under prolonged emotional stress, or when psychogenic manifestations are acute. Proven menopausal benefits are confirmed by the wide clinical acceptance of "Premarin," specifically for the relief of hot flushes and other symptoms of estrogen deficiency, together with the well established tranquilizing efficacy of meprobamate.

Two potencies that will meet the needs of your patients: **PMB-200** — Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 200 mg. of meprobamate. When greater tranquilization is necessary you can prescribe **PMB-400** — Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 400 mg. of meprobamate. Both potencies are available in bottles of 60 and 500.

Ayerst Laboratories New York16,N.Y.
Montreal, Canada

Meprobamate, licensed under U.S. Pat. No. 2,724,720

5916

In over five years o

Proven
in more than
750 published clinical studies

Effective
FOR RELIEF OF ANXIETY
AND TENSION

Outstandingly Safe

For your reference: controlled studies on Miltown...

1. Blumberg, N. *et al.*: Fed. Proc. 17:351, March 1958. **2.** Boyd, L. J. *et al.*: Am. J. Cardiol. 3:229, Feb. 1959. **3.** Brick, H. *et al.*: J. Social Therapy 4:190, 1958. **4.** Bulla, J. D. *et al.*: Am. Pract. & Digest Treat. 10:1961, Nov. 1959. **5.** Ewing, J. A. and Haizlip, T. M.: Am. J. Psychiat. 114:835, March 1958. **6.** Friedman, A. P.: Ann. N. Y. Acad. Sc. 67:822, May 9, 1957. **7.** Greenberg, L. A. *et al.*: Ann. N. Y. Acad. Sc. 67:816, May 9, 1957. **8.** Holliday, A. R.: Northwest Med. 58:837, June 1959. **9.** Hollister, L. E. *et al.*: Dis. Nerv. System 17:289, Sept. 1956. **10.** Laird, D. M. *et al.*: Dis Nerv. System 18:346, Sept. 1957.

©M-2538

s of clinical use...

1 simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation

2 no cumulative effects, thus no need for difficult dosage readjustments

3 does not produce ataxia, change in appetite or libido

4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis

5 does not impair mental efficiency or normal behavior

Usual dosage: One or two 400 mg. tablets t.i.d. *Supplied:* 400 mg. scored tablets, 200 mg. sugar-coated tablets. Also as MEPROTABS®—400 mg. *unmarked,* coated tablets; and as MEPROSPAN®—400 mg. and 200 mg. *continuous release* capsules.

®TRADE-MARK

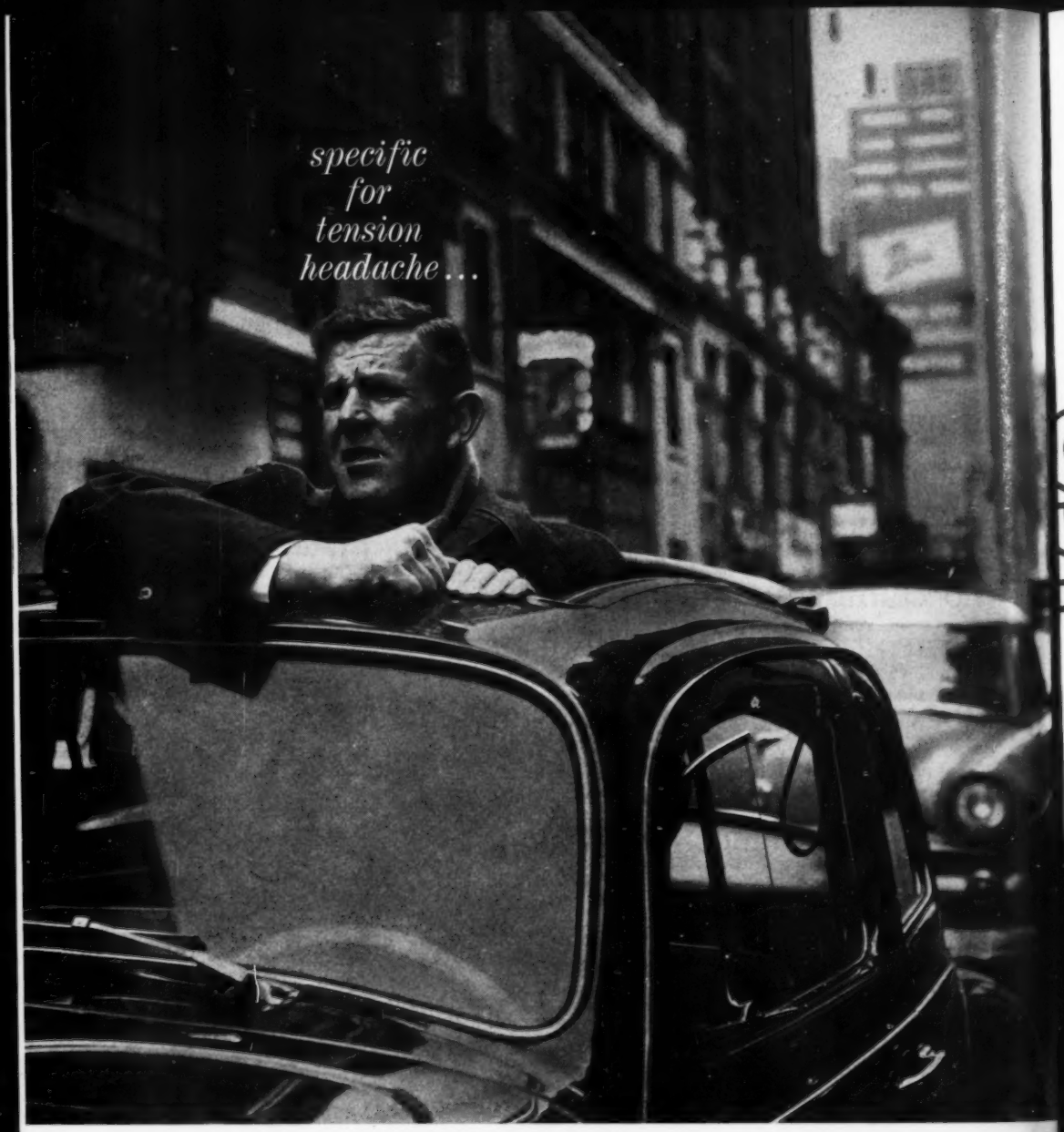
town.....[double-blind]

11. Lasagna, L.: J. Chron. Dis. 3:122, Feb. 1956. 12. Muhlfelder, W. J. *et al.*: Dis. Nerv. System 20:587, Dec. 1959. 13. Pollak, M.: Practitioner 184:231, Feb. 1960. 14. Rickels, K. *et al.*: J.A.M.A. 171:1649, Nov. 21, 1959. 15. Russek, H. I.: Am. J. Cardiol. 3:547, April 1959. 16. Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

Miltown®

meprobamate (Wallace)

WALLACE LABORATORIES / *Cranbury, N. J.*



FIORINAL®

relieves pain,
muscle spasm,
nervous tension

rapid action • non-narcotic • economical

"We have found caffeine, used in combination with acetylsalicylic acid, acetophenetidin, and isobutylallylbarbituric acid, [Fiorinal] to be one of the most effective medicaments for the symptomatic treatment of headache due to tension."
Friedman, A. P., and Merritt, H. H.: J.A.M.A. *163*:1111 (Mar. 30) 1957.

Fiorinal Tablets—***Each tablet contains:*** **Sandoptal (Allylbarbituric Acid N.F. X) 50 mg. (¾ gr.), caffeine 40 mg. (⅔ gr.), acetylsalicylic acid 200 mg. (3 gr.), acetophenetidin 130 mg. (2 gr.).**
Dosage: **1 or 2 tablets every 4 hours, according to need, up to 6 per day.**

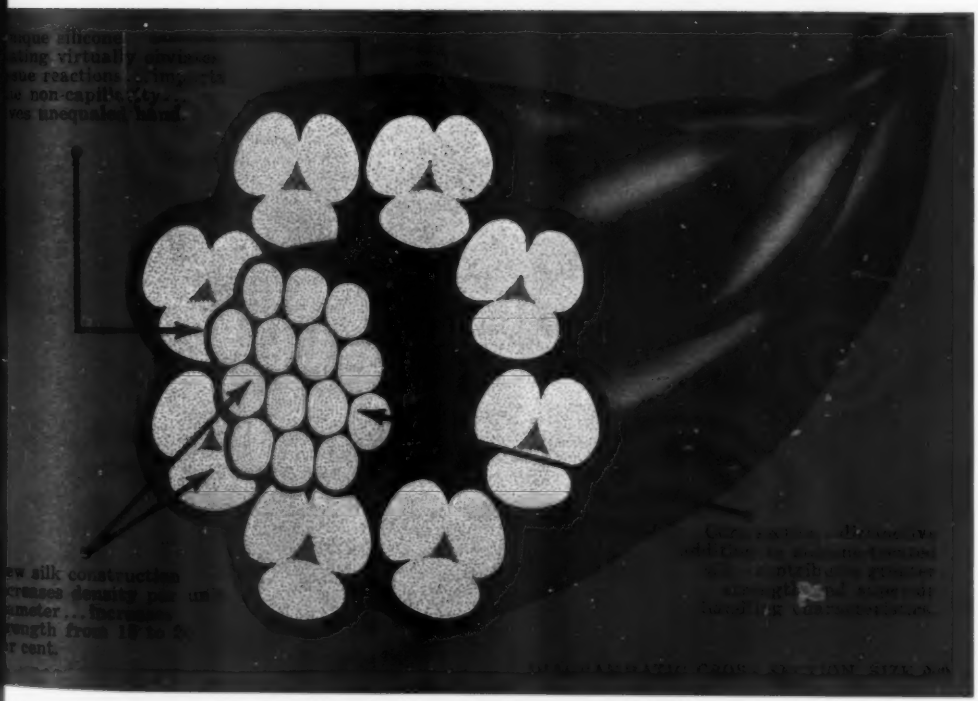
SAN

A SIGNIFICANT NEW RESEARCH DEVELOPMENT FROM

CYANAMID

SURGICAL PRODUCTS DIVISION

SILICONE-TREATED SURGICAL SILK



UPERIOR ON ALL COUNTS TO OTHER EXISTING SILK SUTURES

1 PHYSIOLOGICALLY INERT...

New silicone-rubber coating dramatically overcomes the problem of tissue reactions reported[1-4] with wax-coated silk.

No granuloma, paraffinoma, adhesions, inflammatory reaction or other significant adverse response has been encountered with the surgical use of silicone material.[5-10] Excellent tissue tolerance shortens "lag period," does not inhibit tissue repair. The unique coating process encases all fibers of the suture strand in pure, surgical silicone rubber to present a continuum of physiologically inert suture material to the tissues.

BENIGN RESPONSE TO SILICONE-TREATED SILK

40-day embedment: Thin dense sclero-collagen capsule surrounds suture. No other remarkable findings. No increase in suture volume. (Section cut obliquely to long axis, giving elongation.)

COMMON REACTION TO WAX-COATED SILK

40-day embedment: Moderately thickened sclero-collagen capsule surrounds suture mass. Granulation tissue invaded and increased suture mass by about a factor of 4 over that observed after three days. Many foreign body giant cells on inside of collagen capsule. New blood vessel elements on the border of the capsule.

Mallory's connective tissue stain. Sections cut at 7 microns. Photomicrographs taken at 100x. Suture size: 00

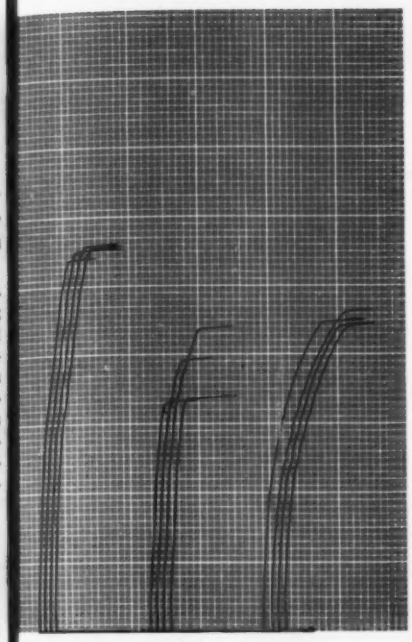
References:

1. Wilkinson, J. F.; Freeman, G.G.; New, N., and Noan, R. D.: Lancet 271:621, 1956. 2. Brown, J. B.; Fryer, M. P., and Lu, M.: A.M.A. Arch Surg. 68:744, 1954. 3. Large,O. P.:Am. J. Surg. 60:415, 1943. 4. Wolf, R.: Ibid. 55:153, 1942. 5. Rosenberg, N.; Moolten, S. E., and Vroman, L.: Arch Surg. 60:363, 1950. 6. Blunt, Jr., W. J.: Am. J. Surg. 95:512, 1958. 7. Lahey, F.: New England J. Med. 240:161, 1949. 8. Dimant, S.: Lancet 267:533, 1954. 9. Rowe, V. K.; Spencer, H. G., and Bass, S. L.: J. Ind. Hygiene & Toxicol. 30:332, 1948. 10. DeNicola, R. R.: J. Urology 63:168, 1950.

SILICONE-TREATED SILK SUTURES

CYANAMID

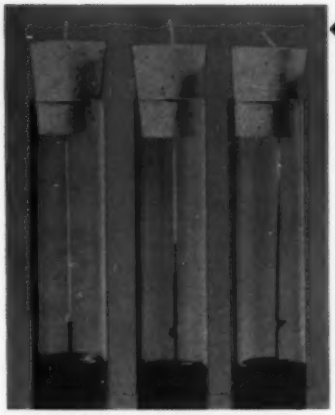
SURGICAL PRODUCTS DIVISION



icone-Treated Silk Tensile Strength Size 000 | Brand A Tensile Strength Size 000 | Brand B Tensile Strength Size 000

2 15% TO 20% GREATER TENSILE STRENGTH

Superiority over other silks is achieved through new, unique braiding process which increases silk density per unit diameter. Added strength may permit selection of smaller size suture in some instances. Silicone coating prolongs *in situ* strength, protects suture against enzymatic or body fluid invasion. Continued tissue-approximation is assured; neo-vascularization and fibrosis are minimized.



Silicone-Treated Silk Size 000 | Brand A Size 000 | Brand B Size 000

3 ABSOLUTE NON-CAPILLARITY

...surpasses all wax-coated silk. Silicone coating prevents "carrier-action" in spread of bacterial contamination along the suture line. The true zero-capillarity has been demonstrated in exacting laboratory tests. The surgical silks tested were subjected to three successive boiling treatments, drying and suspension in dye solution.

The unique construction and silicone-rubber coating provides a balanced "hand" for optimum control in use.

4 EASIEST HANDLING SILK

Surgeons will recognize the balanced "hand" of SILICONE-TREATED SILK as ideally suited to the silk technic of Halsted. The silicone coating imparts both firmness and optimum pliability to the suture strand. The smooth, even silicone coating also minimizes "drag," reduces the extent of suture-induced trauma and will not crack or change under normal handling or varying temperatures.

Available in the SURGILOPE® SP Sterile Suture Strip Pack... in a complete line of pre-cut and Atraumatic® products

SILICONE-TREATED SILK is supplied in the new SURGILOPE SP Sterile Suture Strip Pack which makes possible a safer suture dispensing technique that provides greater protection for patient and personnel. Use of the individual, sterile plastic pack eliminates cut fingers, gloves and breaks in aseptic technique often caused by sharp foil packages or broken glass tubes and jars in O.R.; eliminates need for hazardous jars and irritating jar solutions; saves valuable nurse time and storage space; and permits standardization of suture dispensing through one safer, more efficient meth

NEW SP SERVICE PROGRAM – Significant s ings of nurse time, resterilizing supplies and st age space are now possible with the new SP Serv Program. Unused SURGILOPE SP inner envelo are collected by the O.R. nurse and sent to Surgi Products Division in a special mailing carton su plied free. Sutures from each hospital are separat reprocessed, sterilized and repackaged by indiv ual lot... and the original sutures returned, certifi sterile U.S.P.–at *no* extra cost to the hospital.

SILICONE-TREATED SILK SUTURES

ALSO AVAILABLE NON-STERILE: MEASUROLL® DISPENSER PACKAGE.

Twenty strands per roll.
200 yards (20 x 10 yds.), sizes 5-0 to 0.
600 yards (20 x 30 yds.), sizes 4-0 to 00.

STANDARD SPOOLS

25-yard, sizes 5-0 to 2.
100-yard, sizes 6-0 to 4.

CYANAMID

AMERICAN CYANAMID COMPANY
SURGICAL PRODUCTS DIVISION
30 ROCKEFELLER PLAZA
NEW YORK, N.Y.

SALES OFFICE: DANBURY, CONNECTICUT

PRODUCERS OF DAVIS & GECK SUTURES AND VIM® HYPODERMIC SYRINGES AND NEEDLES

Remarkably effective in the widest range of clinical applications

FOR PAIN

NUMORPHAN®

SUBCUT., I.M., AND RECTAL

In a series[1] of 696 patients, NUMORPHAN* relieved postoperative pain without causing general depression. Nausea due to meperidine "was completely alleviated" by replacement with NUMORPHAN.

"There can be little doubt of the efficacy of Numorphan for the control of pain..."[2]

"During this [two-year] period it has become the narcotic of choice for *short-term* preoperative or postoperative occasions."[3]

1. McInnes, G. F.; Engler, H. S., and Saliba, N. R.: To be published. 2. Samuels, M. L.; Stehlin, J. S.; Dale, S. C., and Howe, C. D.: South. M. J. 52:207, 1959. 3. Coblentz, A., and Bierman, H. R.: New England J. Med. 255:694, 1956.

"A NEW ERA IN PAIN RELIEF"

clinically tested for 5 years/ evaluated in 120 U. S. hospitals/over a quarter of a million doses given/ more than 25,000 patients treated

For Literature on Numorphan, Write

ENDO LABORATORIES
Richmond Hill 18, New York

Endo

U. S. PAT. 2,806,033

Clinical indications for NUMORPHAN

All conditions in which potent analgesia is required, such as:

BEFORE AND AFTER SURGERY

during labor

gastrointestinal, renal, and biliary tract pain

orthopedic manipulations

severe burns and trauma

neoplastic diseases

coronary occlusion with myocardial infarction

pleuritic pain

tabetic crises

radiculitis and other neurologic disorders

Note: Because it possesses little or no cough-inhibiting effect, NUMORPHAN is the drug of choice postoperatively for the patient who requires analgesia but must cough.

Available in 1 and 2 cc. ampuls and 10 cc. multiple-dose vials, 1.5 mg. *l*-14-hydroxydihydromorphinone hydrochloride per cc.; rectal suppositories, 2 mg. and 5 mg. May be habit-forming.

Thanks to your prompt treatment and the smooth action of Deprol, your patient's depression is relieved and her anxiety calmed—*often in two or three days.* She eats properly, sleeps well, and her depression no longer complicates your basic regimen.

Lifts depression...as it calms anxiety!

For pregnant, postpartum and menopausal patients—a smooth, balanced action that lifts depression as it calms anxiety...rapidly and safely

Balances the mood—no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient—*they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation—*they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety.

Acts swiftly—the patient often feels better, sleeps better, within two or three days. Unlike most other antidepressant drugs, Deprol relieves the patient quickly—often within two or three days.

Acts safely—no psychotic reactions. Deprol does not cause hypotension, tachycardia, jitteriness, or liver toxicity. It can be safely administered with basic therapy.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50-light-pink, scored tablets. Write for literature and samples.

▲Deprol▲®

WALLACE LABORATORIES
Cranbury, N. J.

CD-753

DECLOMYCIN®

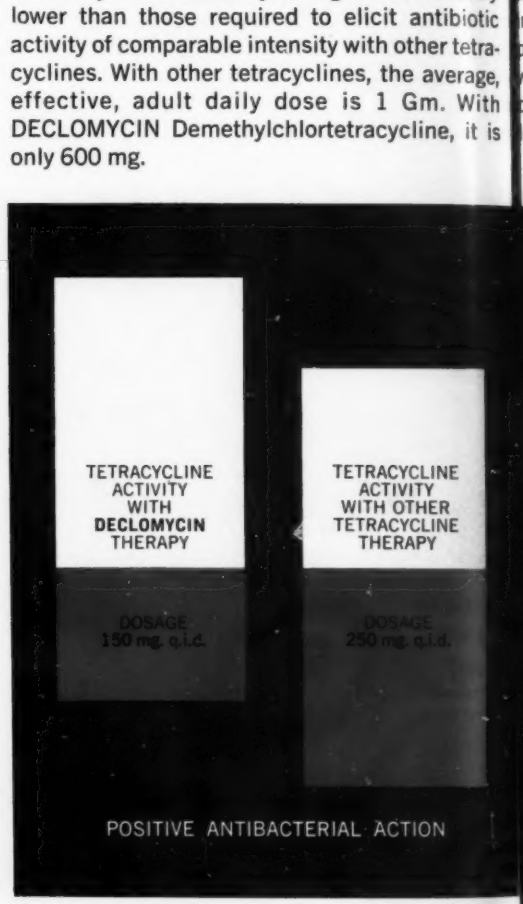
DEMETHYLCHLORTETRACYCLINE LEDERLE

attains
sustains
retains

extra
antibiotic
activity

extra-activity...promptly attained

DECLOMYCIN Demethylchlortetracycline attains—usually within two hours—blood levels more than adequate to suppress susceptible pathogens. These levels are attained in tissues and body fluids on daily dosages substantially lower than those required to elicit antibiotic activity of comparable intensity with other tetracyclines. With other tetracyclines, the average, effective, adult daily dose is 1 Gm. With DECLOMYCIN Demethylchlortetracycline, it is only 600 mg.


TETRACYCLINE ACTIVITY WITH DECLOMYCIN THERAPY
DOSAGE 150 mg. q.i.d.
TETRACYCLINE ACTIVITY WITH OTHER TETRACYCLINE THERAPY
DOSAGE 250 mg. q.i.d.
POSITIVE ANTIBACTERIAL ACTION

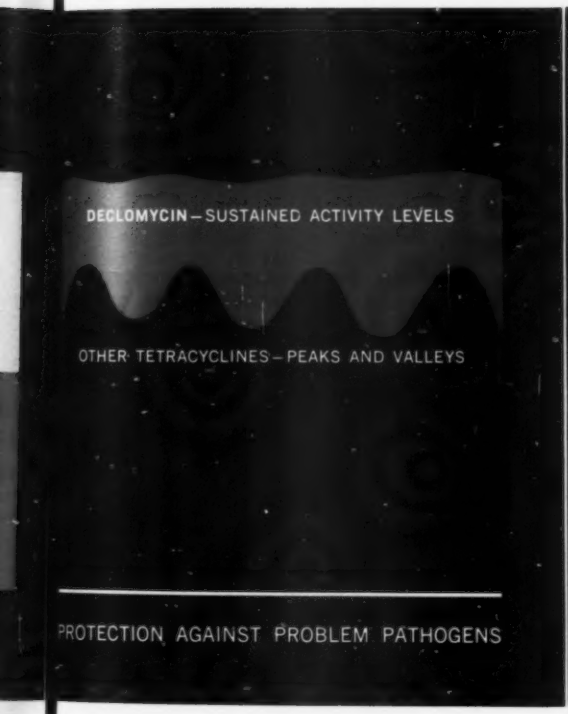
DECLO

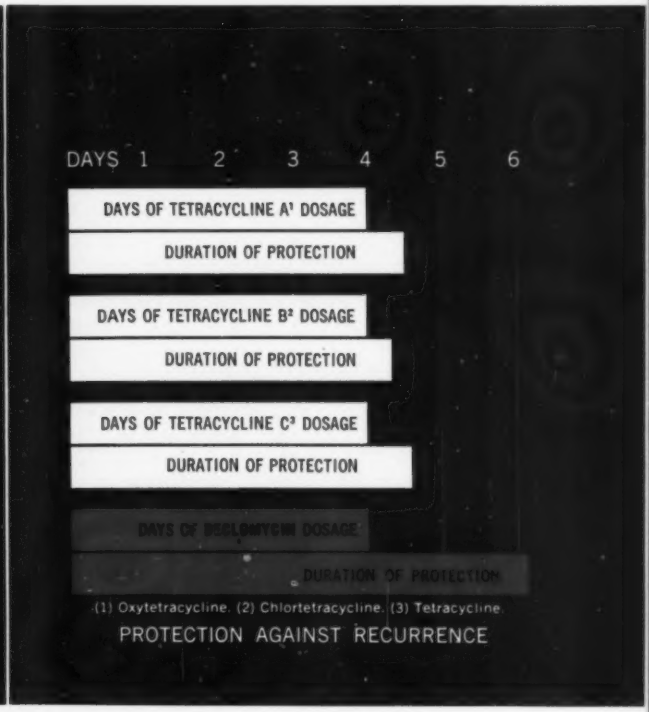
evenly sustained

DECLOMYCIN Demethylchlortetracycline sustains, through the entire therapeutic course, the high activity levels needed to control the primary infective process and to check the onset of a complicating secondary infection at the original—or at another—site. This combined therapeutic action is sustained, in most instances, without the pronounced hour-to-hour, dose-to-dose, peak-and-valley fluctuations in activity levels which characterize other tetracyclines.

long retained

DECLOMYCIN Demethylchlortetracycline retains significant activity levels, up to 48 hours after the last dose is given. At least a full, extra day of positive antibacterial action may thus be confidently expected. One capsule four times a day, for the average adult in the average infection, is the same as with other tetracyclines—but the **total** dosage is lower and the duration of anti-infective action is longer.




DAYS 1 2 3 4 5 6
DAYS OF TETRACYCLINE A¹ DOSAGE
DURATION OF PROTECTION
DAYS OF TETRACYCLINE B² DOSAGE
DURATION OF PROTECTION
DAYS OF TETRACYCLINE C³ DOSAGE
DURATION OF PROTECTION
DAYS OF DECLOMYCIN DOSAGE
DURATION OF PROTECTION
(1) Oxytetracycline. (2) Chlortetracycline. (3) Tetracycline.
PROTECTION AGAINST RECURRENCE

DECLOMYCIN®

DEMETHYLCHLORTETRACYCLINE LEDERLE

- higher activity/intake ratio—positive antibacterial action
- sustained activity levels—protection against problem pathogens
- up to two extra days' activity—protection against recurrence

CAPSULES, 150 mg., bottles of 16 and 100. **Dosage:** Average infections—1 capsule four times daily. Severe infections—Initial dose of 2 capsules, then 1 capsule every six hours.

PEDIATRIC DROPS, 60 mg./cc. in 10 cc. bottle with calibrated, plastic dropper.

Dosage: 1 to 2 drops (3 to 6 mg.) per pound body weight per day—divided into 4 doses.

SYRUP, 75 mg./5 cc. teaspoonful (cherry-flavored), bottles of 2 and 16 fl. oz.

Dosage: 3 to 6 mg. per pound body weight per day—divided into 4 doses.

for the
added measure
of protection
in clinical
practice

PRECAUTIONS: As with other antibiotics, DECLOMYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid exposure to intense sunlight. If adverse reaction or idiosyncrasy occurs, discontinue medication.

Overgrowth of nonsusceptible organisms is a possibility with DECLOMYCIN, as with other antibiotics. The patient should be kept under observation.

DECLOMYCIN®

DEMETHYLCHLORTETRACYCLINE LEDERLE

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

NEW 1960 BOOK

Collins—Fundamentals of Nerve Blocking

By VINCENT J. COLLINS, M.S., M.D.
Associate Professor of Anesthesiology, New York University Medical Center
and Anesthesiologist, Bellevue Hospital Center

With the Assistance of EMERY ANDREW ROVENSTINE, M.D.
Professor of Anesthesiology and Chairman of the Department, New York University Medical Center;
Director, Division of Anesthesia, Bellevue Hospital Center

This is a new, sound and highly dependable guide on when, where, and how to relieve pain by easily applied nerve blocks. Step-by-step regional technics are illustrated by superb anatomical diagrams.

Local anesthetic agents, reactions, needle technic, mechanisms of nerve physiology and other essential facts are considered clearly. Epidural and caudal analgesia, and spinal anesthesia are taken up in separate chapters.

New. 354 Pages. 144 Illustrations. 19 Tables. $9.50

Lewin—The Foot and Ankle

By PHILIP LEWIN, M.D., F.A.C.S., F.I.C.S.
Late Professor of Orthopedic Surgery, Postgraduate
Medical School, Cook County Hospital, Chicago

Dr. Lewin's recognized ability to meet and solve every type of foot and ankle disorder is projected clearly into each page of this book. The clear discussions of causes, diagnosis, prevention, treatment and prognosis are among the reasons the *Jl. A.M.A.* says of the current edition. "Highly recommended as a complete book on the foot and ankle."

Among the many features of the 4th edition are improved techniques, substitutions, transpositions and rehabilitative procedures involving bones, tendons and blood vessels. Recently accepted surgical procedures for poliomyelitis, tendon transfers, and bunions are presented, as well as many other commonly used surgical procedures.

4th Edition. 612 Pages. 339 Illustrations. $14.00

Joslin—Treatment of Diabetes Mellitus

By ELLIOTT P. JOSLIN, M.D. PRISCILLA WHITE, M.D.
HOWARD F. ROOT, M.D. and ALEXANDER MARBLE, M.D.
New England Deaconess Hospital, Boston

This classic work by renowned authorities is one of the most useful books available on the understanding, diagnosis and treatment of diabetes mellitus. It is based on experiences in treating more than 51,000 diabetics, including 1700 pregnant patients.

Special attention is paid to exercise, diet, the use of insulin, and diagnosis and care of complications. Oral use of the sulfonylureas is reported, with succinct rules for their use and summaries of treatment based on several thousand cases.

10th Edition. 798 Pages. Illustrated. One Plate in Color. 153 Tables. $16.50

LEA & FEBIGER WASHINGTON SQUARE, PHILADELPHIA 6, PA.
Canadian Agent: The Macmillan Co. of Canada Ltd., 70 Bond St., Toronto

Send books indicated: ☐ Check enclosed. ☐ Bill me at 30 days. ☐ Charge on your easy payment plan.

We pay postage if remittance in full accompanies your order.

☐ Collins—Fundamentals of Nerve Blocking.....$9.50

☐ Lewin—The Foot and Ankle.....$14.00 ☐ Joslin—Treatment of Diabetes Mellitus.....$16.50

Dr. (Please print).....Address.....

City.....Zone.....State.....

S. G. & O. 12-60

introducing

a completely new

water-soluble salt

of FURADANTIN

NEW FURADANTIN® SODIUM

brand of nitrofurantoin

for Intravenous Use

where oral medication is not feasible

for treating

genitourinary infections, such as

pyelonephritis, pyelitis, cystitis, prostatitis

systemic, bacterial infections

has been lifesaving in certain instances

(COPY OF PACKAGE INSERT)

FURADANTIN®

brand of nitrofurantoin

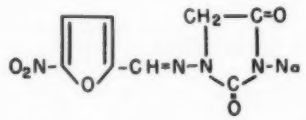
SODIUM

STERILE

For Intravenous Use

ACTIVE INGREDIENT: Each vial contains sufficient material to permit withdrawal of 180 mg. Furadantin, as the sodium salt.

Furadantin Sodium is a synthetic antibacterial agent, one of the antimicrobial nitrofurans, having the following structure:



1-(5-nitrofurfurylideneamino)-hydantoin sodium

INDICATIONS: The antibacterial spectrum of Furadantin encompasses gram-negative organisms such as E. coli, K. pneumoniae and certain strains of Proteus sp., Pseudomonas sp., and Aerobacter sp.; as well as gram-positive organisms such as staphylococci, streptococci, pneumococci, Clostridium sp., B. subtilis.

Furadantin Sodium is indicated in genitourinary infections such as pyelonephritis, pyelitis, cystitis and prostatitis, when the oral form is not feasible. It is also indicated in systemic bacterial infections with the exception of septicemias (bacteremias) unless other therapy has failed or until further work has demonstrated its activity in this condition caused by organisms sensitive in vitro to Furadantin.

In genitourinary tract infections, peroral therapy should replace intravenous when possible. It is not intended to replace surgery when mechanical obstruction or stasis is present.

ADMINISTRATION AND DOSAGE: The crystals must be dissolved just prior to use as follows: Add 15 cc. of 5% Dextrose Injection, USP, or Water for Injection, USP, to the vial of dry sterile Furadantin Sodium. Empty the syringe forcefully. Shake well to insure complete solution.

FURTHER DILUTION IS REQUIRED
BASED UPON THE PATIENT'S WEIGHT:

Patients weighing over 120 pounds. The recommended dose is 180 mg. of Furadantin in 500 cc. of diluent, twice daily. This is prepared as follows: Withdraw the solution of 180 mg. of Furadantin from the vial and add it to 500 cc. of 5% Dextrose in water, 5% Dextrose in Saline, Normal Saline or 1/6 molar Sodium Lactate intravenous solution. This final solution is to be given by intravenous drip at the usual rate.

Patients weighing under 120 pounds. The recommended dose is 3 mg./lb. of body weight per day divided in two equal doses. This is calculated on the basis that when the Furadantin Sodium in each vial is dissolved in 15 cc. of diluent, each cc. of solution represents 12 mg. of Furadantin. To prepare the final solution, each cc. of the initial Furadantin dilution should be added to a minimum of 33 cc. of parenteral fluid.

CAUTION: In the presence of impairment of renal function or acidosis administer Furadantin Sodium intravenously with caution as with any potent antibacterial agent. If employed under such circumstances the blood pH, CO_2 content or combining power and urea nitrogen or non-protein nitrogen should be followed closely.

The occurrence of a few cases of hemolytic anemia during Furadantin therapy has appeared in the literature.* A small percentage of negroes and ethnic groups of Mediterranean and Near-Eastern origin has an intrinsic abnormality of the red blood cells. As a result, hemolysis may occur with fava beans and certain drugs, such as primaquine. Thus it is advisable to closely observe such patients receiving Furadantin and to discontinue its administration if there is any indication of this condition developing.

SIDE REACTIONS: If nausea or emesis occur, these may be minimized by slowing the rate of administration, or by decreasing the dosage.

Sensitization occurs rarely in the form of an erythematous, maculopapular cutaneous eruption or urticaria. This is readily controlled by discontinuing treatment.

Occasionally a patient may show minor side reactions such as headache or malaise. No stomatitis, colitis, proctitis, anal pruritus or hematopoietic, renal or hepatic toxicity, have been reported with Furadantin Sodium.

PACKAGING: Sterile 20 cc. vials, containing one adult dose of crystalline sterile Furadantin Sodium (equivalent to 180 mg. of Furadantin).

CAUTION: Federal Law prohibits dispensing without prescription.

NOTE: DO NOT ADMINISTER INTRAMUSCULARLY. DO NOT USE WITHOUT DILUTING. MIX JUST PRIOR TO USE.

*West, M. and Zimmerman, H. H.: Hemolytic Anemia in Patient Receiving Nitrofurantoin (Furadantin), J.A.M.A. 162:637 (Oct. 13) 1956. Kimbro, E. L., Jr.: Sachs, M. F.; and Torbert, J. V. Jr.: Mechanism of Hemolytic Anemia Induced by Nitrofurantoin (Furadantin), Fed. Proc. 16:312 (Mar.) 1957.

EATON LABORATORIES
Division of The Norwich Pharmacal Company
NORWICH, NEW YORK

THE NITROFURANS—a *unique* class of antimicrobials

A NEW INDEX TO

SURGERY
Gynecology & Obstetrics

With International Abstracts of Surgery

Volumes 101 to 110
July 1955 through June 1960
in blue buckram binding, gold stamped
priced at $10.00

THE fourth cumulative index to SURGERY, GYNECOLOGY & OBSTETRICS covers Volumes 101 to 110—July 1955 through June 1960. All original articles, editorials, special sections—such as The Book Shelf, The Surgeon at Work—as well as the Collective Reviews appearing in the INTERNATIONAL ABSTRACTS OF SURGERY during this five year period have been indexed and cross-indexed to make all the material easily and readily accessible to the user.

Please send me _____ copies of the INDEX TO VOLUMES 101 TO 110 at $10.00 per copy.

I enclose _____.

(Add 25¢ for mailing expense outside U.S.A.)

Doctor_____

Address_____

City_____ _____Zone_____State_____

SURGERY, *Gynecology & Obstetrics*
54 EAST ERIE STREET, CHICAGO 11, ILLINOIS

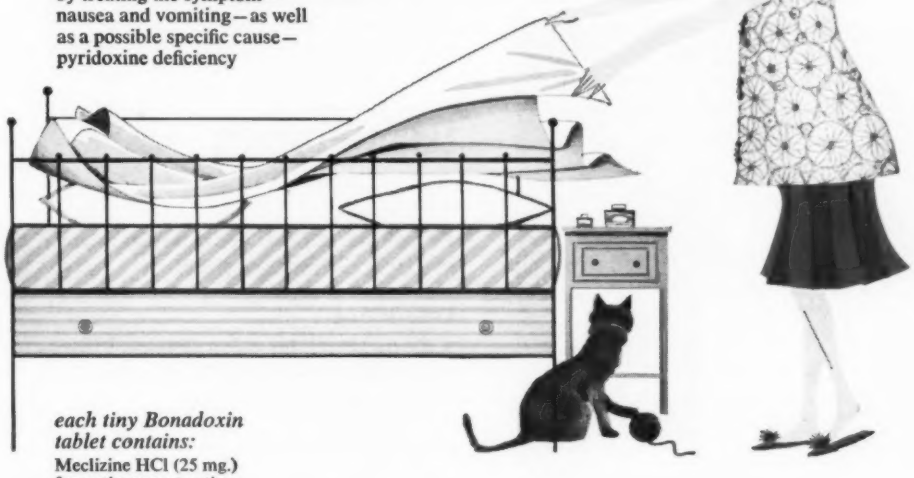
taken at bedtime

BONADOXIN®

STOPS MORNING SICKNESS IN 94%

OFTEN WITH JUST ONE TABLET DAILY

by treating the symptom—nausea and vomiting—as well as a possible specific cause—pyridoxine deficiency



each tiny Bonadoxin tablet contains:
Meclizine HCl (25 mg.) for antinauseant action
Pyridoxine HCl (50 mg.) for metabolic replacement.

usual dose: One tablet at bedtime; severe cases may require another tablet on arising.

supply: Bottles of 25 and 100 tablets. Bonadoxin also effectively relieves nausea and vomiting associated with: anesthesia, radiation sickness, Meniere's syndrome, labyrinthitis, and motion sickness. Also useful in postoperative nausea and vomiting.

Bibliography on request.

For infant colic, try Bonadoxin Drops. Each cc. contains: Meclizine 8.33 mg./ Pyridoxine 16.67 mg.

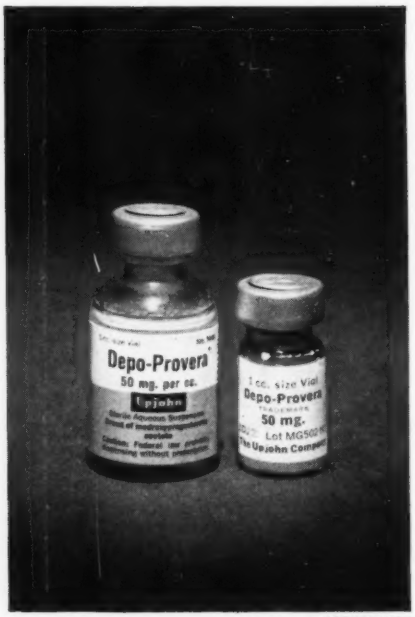
New York 17, N.Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being™

and...when your OB patient needs the best in prenatal vitamin-mineral supplementation...

OBRON®

In threatened abortion...

Provera* is now available in a new long-acting injectable form:



ACTUAL SIZE

Depo-Provera**

Potent

Depo-Provera is 4 times as potent as any other available progestogen (by castrate assay).

Long-acting

A single 50 mg. injection of Depo-Provera will produce a progestational effect that lasts for up to 16 days.

Well tolerated

No significant untoward side effects have been reported.

More acceptable to patient

Micronized in sterile aqueous suspension—little or no pain at site of injection.

Formula:

Sterile micronized medroxyprogesterone acetate (17-alpha-hydroxy-6-alpha-methylprogesterone acetate).

Supplied:

In 1 cc. and 5 cc. size vials.

Depo-Provera

Upjohn

*TRADEMARK, REG. U.S. PAT. OFF. **TRADEMARK

The Upjohn Company, Kalamazoo, Michigan

Infectious folliculitis with secondary impetiginization treated with* FURACIN-HC Cream *—6 days later improved and discharged.

Pyodermas: fight infection, facilitate healing

In clinical use for more than 13 years and today the most widely prescribed single topical antibacterial, FURACIN *retains undiminished potency against pathogens such as staphylococci that no longer respond adequately to other antimicrobials.* FURACIN *is gentle, nontoxic to regenerating tissue, speeds healing through efficient prophylaxis or prompt control of infection. Unique water-soluble bases provide thorough penetration, lasting activity in wound exudates, without "sealing" the lesion or macerating surrounding tissue.*

the broad-spectrum bactericide exclusively for topical use

FURACIN®

brand of nitrofurazone

in dosage forms for every topical need

Soluble Dressing / Soluble Powder
Solution / Cream / HC Cream
(with hydrocortisone) / Vaginal
Suppositories / Inserts / FURESTROL®
Suppositories (with diethylstilbestrol)
Special Formulations for Eye, Ear, Nose

EATON LABORATORIES
Division of The Norwich Pharmacal Company
NORWICH, NEW YORK

a pair of gynecologic patients:

both are free of pain—but only one is on

DILAUDID®

(Dihydromorphinone HCl)

swift, sure analgesia normally unmarred by nausea and vomiting

DILAUDID provides unexcelled analgesia before and after gynecologic, obstetric and surgical procedures. Its high therapeutic ratio is commonly reflected by lack of nausea and vomiting — and marked freedom from dizziness, somnolence, anorexia and constipation.

▲ by mouth ▲ by needle ▲ by rectum

2 mg., 3 mg., and 4 mg.

May be habit forming—usual precautions should be observed as with other opiate analgesics.

KNOLL PHARMACEUTICAL COMPANY • ORANGE, NEW JERSEY

"T
kar
tho
res
ant
on
wh

Inf
con

SU
(a
1.0

B

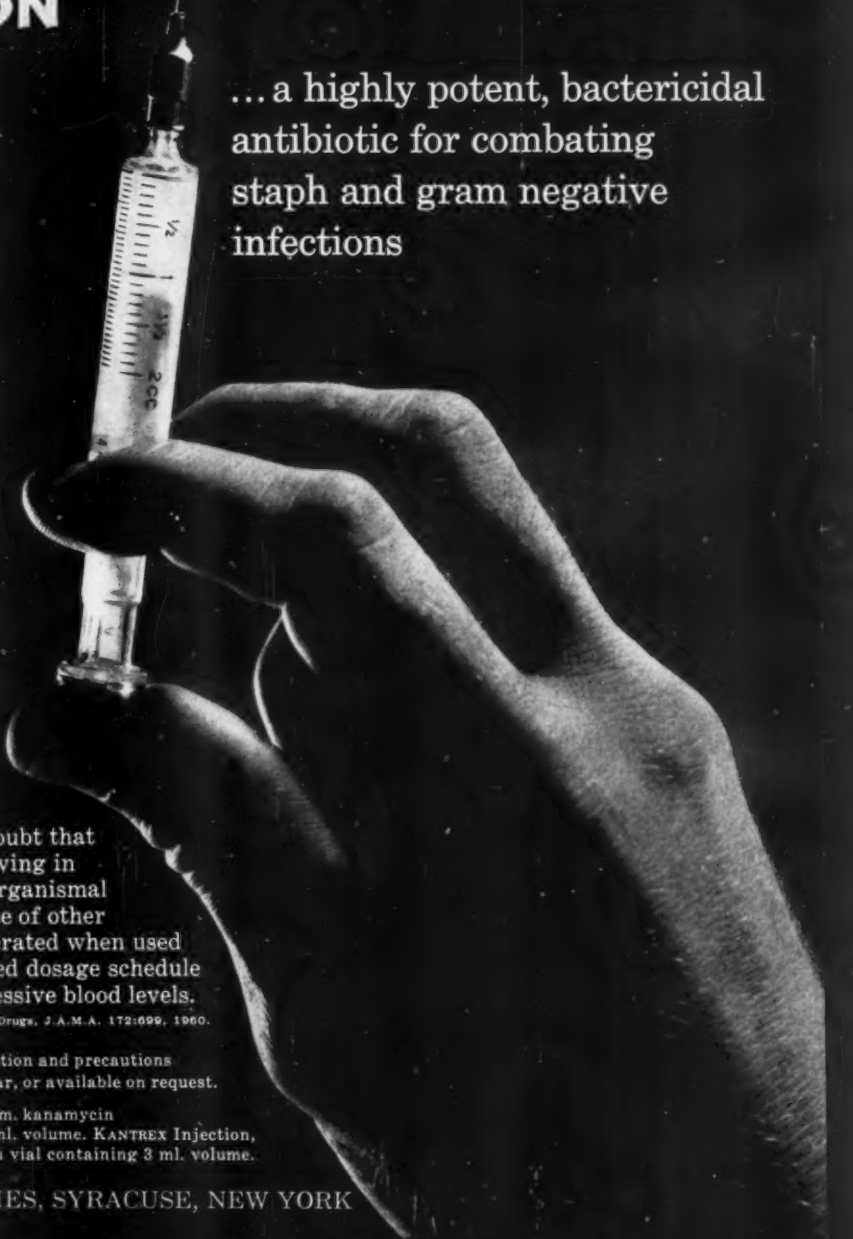
"life saving" in many cases...

KANTREX®

Kanamycin Sulfate Injection

INJECTION

...a highly potent, bactericidal antibiotic for combating staph and gram negative infections



"There appears to be no doubt that kanamycin has been lifesaving in those instances in which organismal resistance precludes the use of other antimicrobials."* Well tolerated when used on a properly individualized dosage schedule which does not induce excessive blood levels.

*Council on Drugs. J.A.M.A. 172:699, 1960.

Information on dosage, administration and precautions contained in official package circular, or available on request.

SUPPLY: KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in vial containing 2 ml. volume. KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in vial containing 3 ml. volume.

BRISTOL LABORATORIES, SYRACUSE, NEW YORK

B-D

skilled
hands deserve
the finest

WILSON SURGEONS' GLOVES

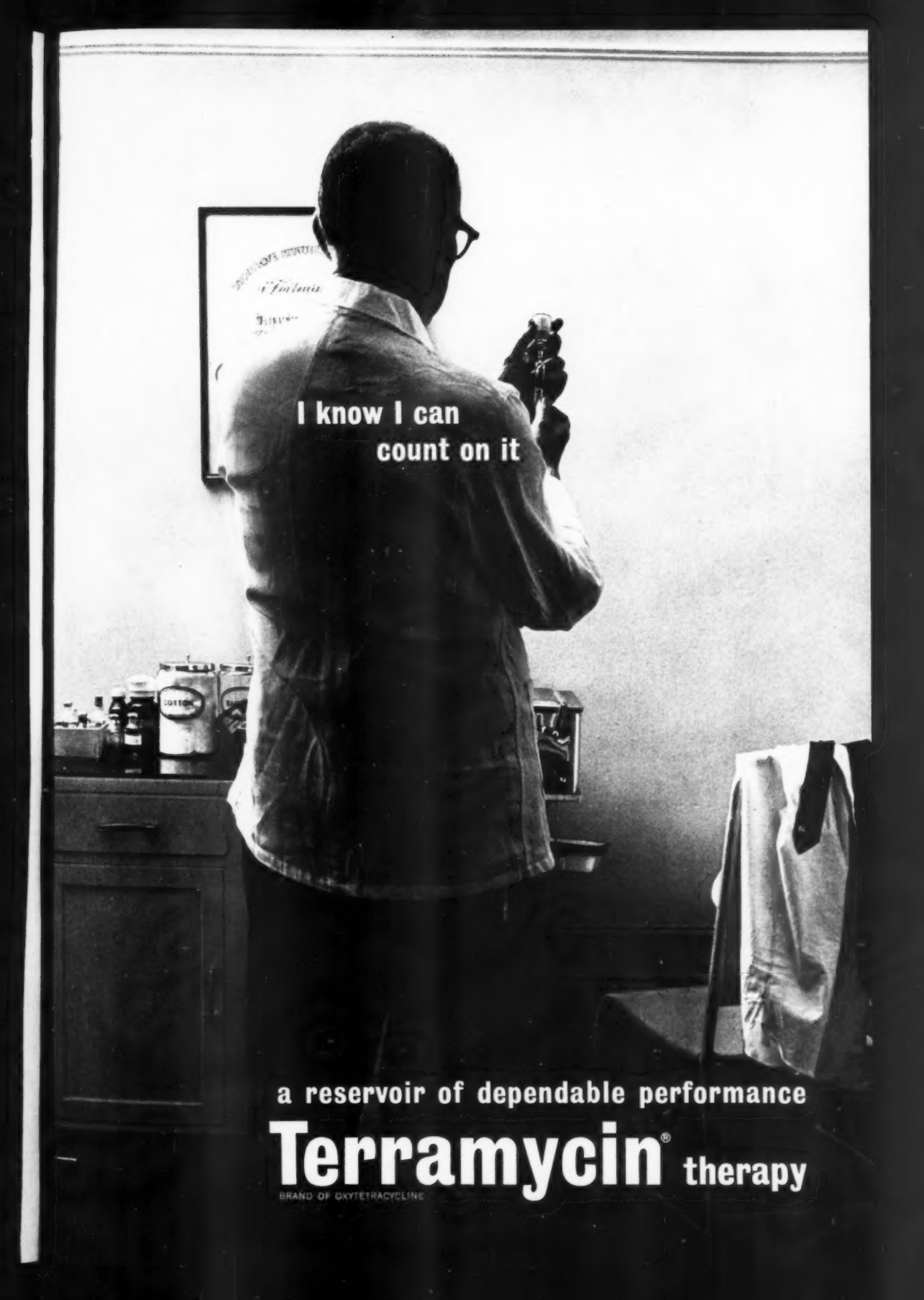
THE ONLY BRAND WITH
flat trim wrist and naturally curved fingers

Now available in a new wrist style—without beaded edge—color-banded Wilson Gloves are better than ever. They slip on more easily, fit the wrist more comfortably, show less tendency to roll down in use. And with exclusive curved fingers that follow natural hand conformation, Wilson Surgeons' Gloves are unsurpassed in fit and comfort.

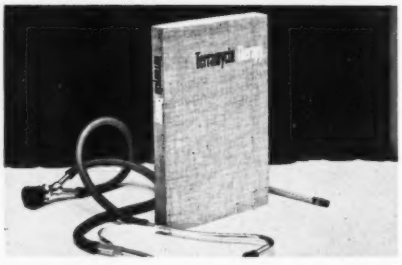
BECTON, DICKINSON AND COMPANY
RUTHERFORD, NEW JERSEY
in Canada: Becton, Dickinson & Co., Canada, Ltd., Toronto 10, Ontario

WILSON AND B-D—REGISTERED TRADEMARKS, U.S. PAT. OFF.

80060


I know I can
count on it
a reservoir of dependable performance
Terramycin® therapy
BRAND OF OXYTETRACYCLINE

now—in addition to dependable effectiveness and excellent toleration...



dosage flexibility and economy

Terramycin®

BRAND OF OXYTETRACYCLINE

INTRAMUSCULAR SOLUTION

now available new 10 cc. multi-dose vial

Science for the world's well-being™

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

IN BRIEF

The dependability of Terramycin is based on broad antimicrobial effectiveness, excellent toleration, and low order of toxicity. Terramycin Intramuscular Solution, a *preconstituted* parenteral form of oxytetracycline with 2% Xylocaine* as a local anesthetic, facilitates prompt initiation of broad-spectrum antibiotic therapy when, in the judgment of the physician, immediate oral administration is inconvenient or impractical. There is a notably low incidence of irritation or pain at the injection site. In an experimental study,† injection of Terramycin Intramuscular Solution produced the smallest amount of local tissue reaction as compared to other intramuscular broad-spectrum antibiotic preparations.

Now—the availability of a *new multi-dose* 10 cc. vial permits *dosage flexibility* and *economy* hitherto possible only with narrow-spectrum antibiotics. This is an advantage of particular value in pediatrics, where variations in age, weight, and severity of illness require individual dosage adjustment.

INDICATIONS: All oxytetracycline indications whenever initial or continuing therapy with I.M. injection is indicated. Compatible oral therapy may then be given with Cosa-Terramycin® Capsules, Cosa-Terrabon® Oral Suspension or Pediatric Drops. Effective against both gram-positive and gram-negative bacteria, rickettsiae, spirochetes, and large viruses, Terramycin therapy is indicated in a great variety of infections due to susceptible organisms, e.g., infections of the respiratory, gastrointestinal, and genitourinary tracts, surgical and soft-tissue infections, ophthalmic and otic infections, and many others.

ADMINISTRATION AND DOSAGE: For intramuscular injection only. Adults: Unless otherwise specified, a dose of 100 mg. every 8-12 hours, or a single daily dose of 250 mg. should be adequate for most mild or moderately severe infections. In *severe* infections, 100 mg. every 6-8 hours or 250 mg. every 12 hours may be necessary. Infants and children should receive proportionately less in accordance with age and weight of patient, and severity of infection.

SIDE EFFECTS AND PRECAUTIONS: Aside from occasional mild pain at injection site, adverse reactions (including allergic) have been rare. As with all I.M. preparations, injection should be made within the body of a relatively large muscle. After insertion of needle, aspiration should be attempted before injecting to avoid inadvertent administration into a blood vessel; care should always be taken to avoid injecting into a major nerve or its surrounding sheath. Subcutaneous and fat-layer injection may cause mild pain and induration, which may be relieved by an ice pack.

Use of antibiotics may result in an overgrowth of nonsusceptible organisms—particularly monilia and resistant staphylococci. If a new infection caused by a resistant pathogen appears, discontinue the medication and institute appropriate specific therapy as indicated by susceptibility testing.

SUPPLIED: *Terramycin Intramuscular Solution* is available in a new 10 cc. multi-dose vial, providing five 2 cc. doses, 50 mg./cc., also available as 2 cc. prescored glass ampules, containing 100 mg. or 250 mg., packages of 5 and 100. For rapidly fulminating or critical infections—*Terramycin Intravenous*, in vials of 250 mg. and 500 mg. (buffered with 1 Gm. and 2 Gm. ascorbic acid, respectively). Available for oral therapy: *Cosa-Terramycin® Capsules*, 250 mg. and 125 mg.; *Cosa-Terrabon® Oral Suspension* (preconstituted), 125 mg. per 5 cc. teaspoonful, in bottles of 2 oz. and 1 pint; *Cosa-Terrabon® Pediatric Drops* (preconstituted), 5 mg. per drop (100 mg. per cc.), bottle of 10 cc. with calibrated plastic dropper. In addition, a variety of other systemic and local dosage forms are available to meet specific therapeutic requirements.

More detailed professional information available on request.

*XYLOCAINE® IS THE TRADEMARK OF ASTRA PHARMACEUTICAL PRODUCTS, INC. FOR ITS BRAND OF LIDOCAINE.

†*Hanson, D.: Tissue Reaction from Injected Antibiotics, Scientific Exhibit, Annual Meet., Am. Soc. Clin. Pathologists, Chicago, Sept., 1960.*

thanks to

DESITIN®

hemorrhoidal

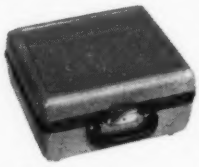
SUPPOSITORIES

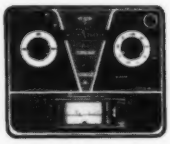
with cod liver oil

Samples and literature available from

DESITIN CHEMICAL COMPANY • 812 Branch Ave., Providence 4, R. I.

18 pounds, instrument and accessories

Brief-case size 

Simple, straightforward  operation

Lightweight, unequalled portability

Complete diagnostic accuracy

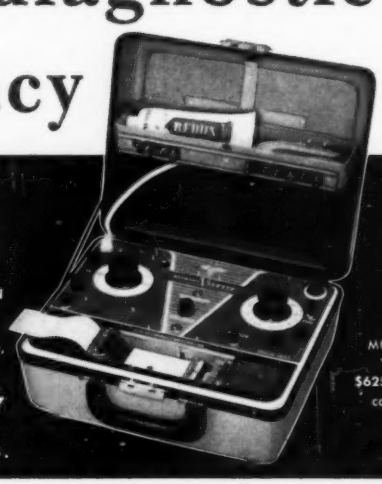
MODEL 300

VISETTE

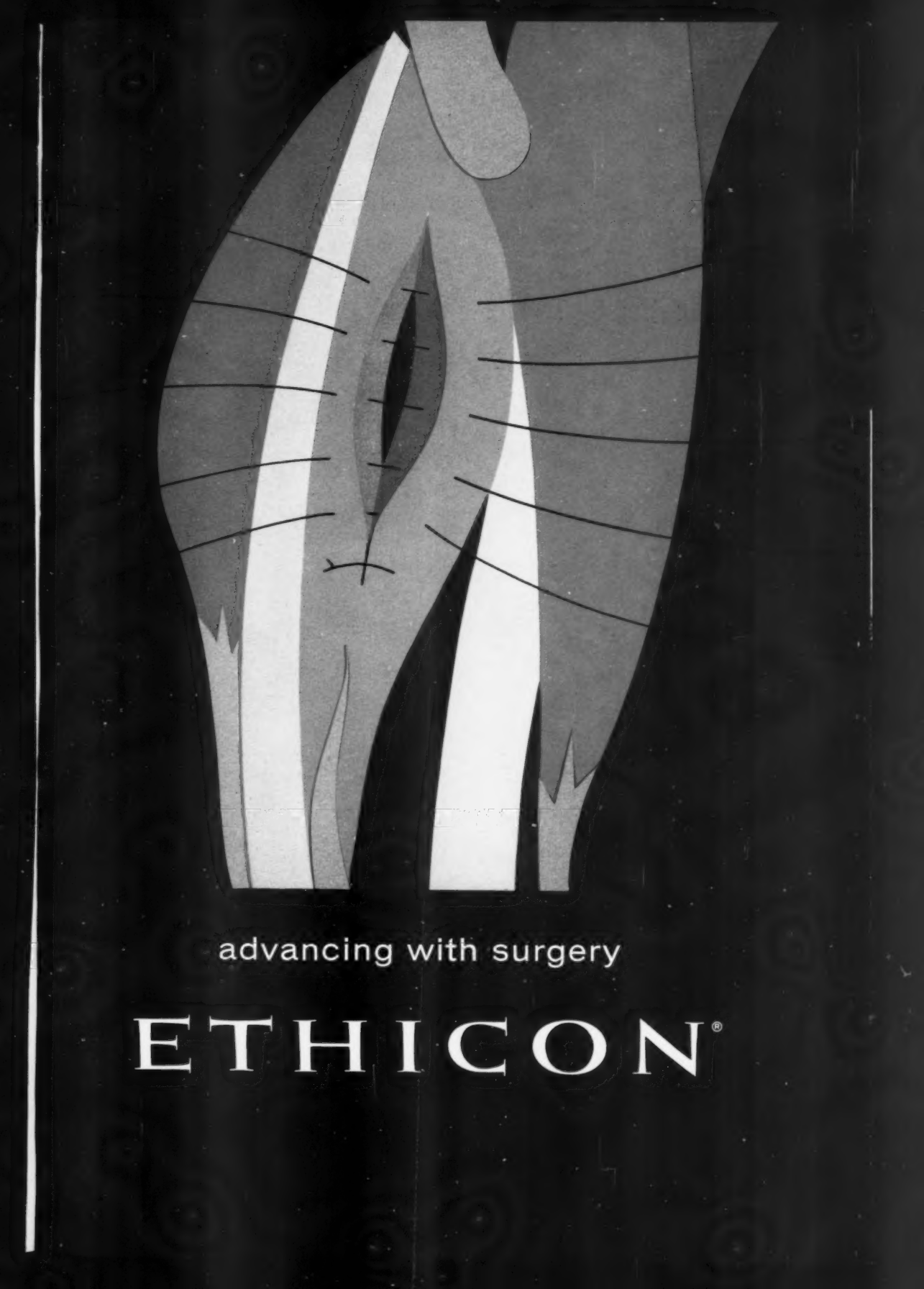
ONE OF THREE PRECISION* ELECTROCARDIOGRAPHS MADE BY SANBORN

Ask your local Sanborn Branch Office or Service Agency man (42 cities throughout the country), for a demonstration or descriptive literature

SANBORN COMPANY
MEDICAL DIVISION
175 WYMAN ST., WALTHAM 54, MASS.



MODEL 300 VISETTE $625 delivered, continental U. S. A.


advancing with surgery
ETHICON®

collagen-pure
surgical gut

ETHICON®

Amsco...

Sonic Energy Systems

Method-engineered for the fast, critical cleaning of surgical instruments, syringes and related items

Isn't it time your hospital studied the benefits of this advanced technic?

Write for newly-published technical brochure MC-564

·AMSCO·
ELECTRONICS
A Division of AMERICAN STERILIZER COMPANY · Erie, Pa.

World's largest designer and manufacturer of Sterilizers, Surgical Tables, Lights and related technical equipment

NOW–for more comprehensive control of

'pain & spasm'

- pain due to or associated with
- spasm of skeletal muscle

a NEW Robins *muscle relaxant-analgesic*

Robaxisal®

ROBAXIN® WITH ASPIRIN

ROBAXISAL, a new dual-acting muscle relaxant-analgesic, effectively treats both skeletal muscle spasm and severe pain due to or associated with the spasm. Each Tablet contains:

- A relaxant component — Robaxin* — widely recognized for its prompt, long-lasting relief of painful skeletal muscle spasm, with unusual freedom from undesired side effects. . . . . 400 mg.

*Methocarbamol 'Robins' U.S. Pat. No. 2770649.

- An analgesic component—aspirin—whose pain-relieving effect is markedly enhanced by Robaxin, and which has added value as an anti-inflammatory and anti-rheumatic agent. . . . (5 gr.) 325 mg.

SUPPLY: ROBAXISAL Tablets (pink-and-white, laminated) in bottles of 100 and 500.
Also available: ROBAXIN Injectable, 1.0 Gm. in 10-cc ampul. ROBAXIN Tablets, 0.5 Gm. (white, scored) in bottles of 50 and 500.

. . . or when anxiety accompanies pain and spasm: **ROBAXISAL®-PH** (Robaxin® with Phenaphen®). Sedative-enhanced analgesic and skeletal muscle relaxant. Each two white-and-green laminated ROBAXISAL-PH tablets contain: methocarbamol 800 mg., plus the equivalent of one Phenaphen capsule (phenacetin 194 mg., acetylsalicylic acid 162 mg., hyoscyamine sulfate 0.031 mg., and ¼ gr. phenobarbital 16.2 mg.). Bottles of 100 and 500.

A. H. ROBINS CO., INC., Richmond 20, Va.

Making today's medicines with integrity . . . seeking tomorrow's with persistence

faster recovery, greater comfort for your OB-GYN patients

Administered before and after cervicovaginal surgery, irradiation, delivery, and office procedures such as cauterization, FURACIN CREAM promptly controls infection; reduces discharge, irritation and malodor; hastens healing. FURACIN CREAM is active in the presence of exudates, yet is nontoxic to regenerating tissue, does not induce significant bacterial resistance nor encourage monilial overgrowth.

FURACIN® CREAM

BRAND OF NITROFURAZONE

FURACIN 0.2% in a fine cream base, water-miscible and self-emulsifying in body fluids. Tubes of 3 oz., with plastic plunger-type vaginal applicator. Also available: FURACIN Vaginal Suppositories.

THE NITROFURANS—a *unique* class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

NEW PROTEIN TISSUE-BUILDING AGENT

ADROYD® N+

oxymetholone
Parke-Davis

FOR SIGNIFICANT ANABOLIC GAINS IN: ASTHENIA (UNDERWEIGHT, ANOREXIA, LACK OF VIGOR); CONVALESCENCE FROM SURGERY OR SEVERE INFECTIONS; WASTING DISEASES; BURNS; FRACTURES; OSTEOPOROSIS; AND IN OTHER CATABOLIC STATES

■ PROMOTES AND MAINTAINS POSITIVE NITROGEN BALANCE ■ HELPS RESTORE APPETITE, STRENGTH, AND VIGOR ■ BUILDS FIRM, LEAN MUSCULAR TISSUE ■ FAVORABLY INFLUENCES CALCIUM AND PHOSPHORUS METABOLISM ■ PROMOTES A SENSE OF WELL-BEING

ADROYD PROVIDES HIGH ANABOLIC ACTIVITY – The tissue-building potential of ADROYD exceeds its androgenic action to the extent that masculinizing effects have not been a problem in clinical use.* Other advantages of ADROYD are: Neither estrogenic nor progestational. No significant fluid retention. Apparent freedom from nausea, vomiting, and other gastrointestinal disturbances. Effective by the oral route.

See medical brochure, available to physicians, for details of administration and dosage.

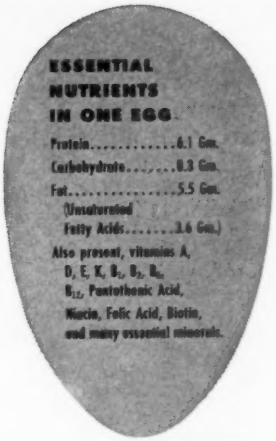
Supplied: 10-mg. scored tablets, bottles of 30. 48748

*Reports to Department of Clinical Investigation, Parke, Davis & Company, 1958 and 1959.

PARKE-DAVIS

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

all this... and only 77 calories



Few foods known to man provide a higher ratio of nutrient value to calories than do eggs.

The quality of egg protein is a standard against which the proteins of other foods are measured.

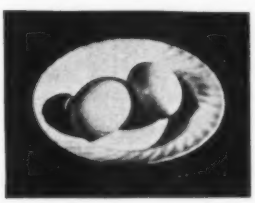
The cholesterol and fatty acid contents of two eggs—traditionally a widely preferred breakfast—fit well into the daily diet, even when lessened fat intake is recommended.

Because of their high nutrient value, their easy digestibility, compatibility, and nutritional complementation of other foods, eggs are included in the recommended dietary* for many conditions in which diet adjustment is indicated.

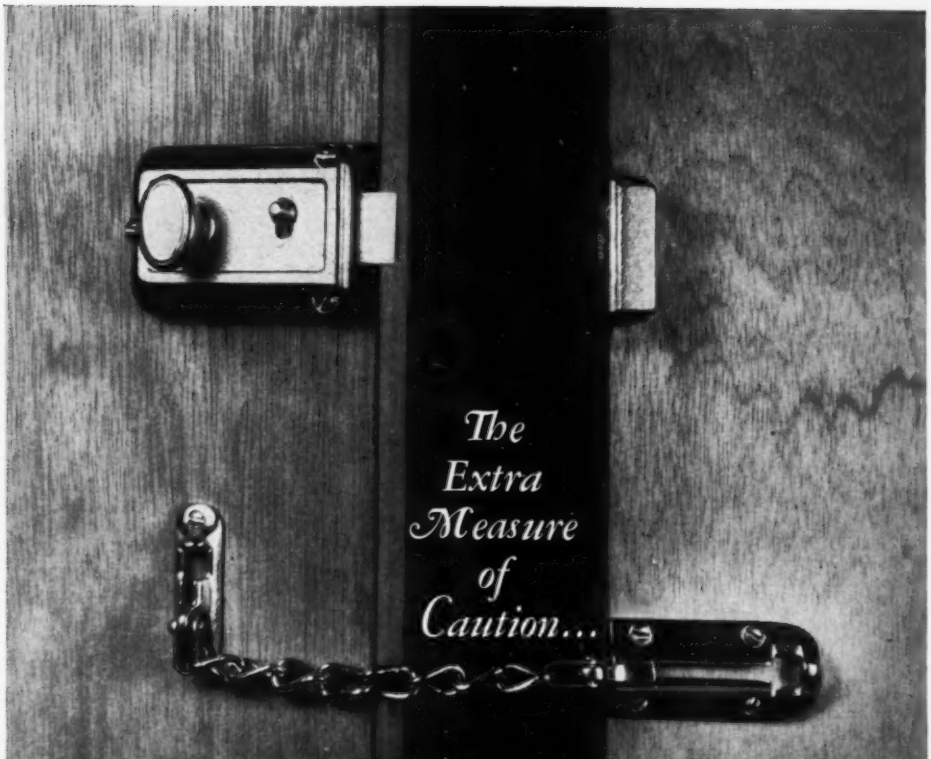
Eggs are listed in the daily recommendations of nourishing liquid, restricted fiber, low sodium, restricted purine, low-calorie, and many other diets.

**Recommended in the diet manuals of teaching institutions.*

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.



Poultry and Egg National Board
8 South Michigan Avenue, Chicago 3, Illinois



Tetracycline now combined with the new, more active antifungal antibiotic – Fungizone – for broad spectrum therapy / antimonilial prophylaxis

A new advance in broad spectrum antibiotic therapy, MYSTECLIN-F provides all the well-known benefits of tetracycline and also contains the new, clinically proved antifungal antibiotic, Fungizone. This Squibb-developed antibiotic, which is unusually free of side effects on oral administration when given in oral prophylactic doses, has substantially greater in vitro activity than nystatin against strains of Candida (Monilia) albicans.

Thus, in addition to providing highly effective broad spectrum therapy, MYSTECLIN-F prevents the monilial overgrowth in the gastrointestinal tract so commonly associated with such therapy. It helps to protect the patient from troublesome, even serious, monilial complications.

New Mysteclin-F provides this added antifungal protection at little increased cost to your patients over ordinary tetracycline preparations.

Available as: MYSTECLIN-F CAPSULES (250 mg./50 mg.) MYSTECLIN-F HALF STRENGTH CAPSULES (125 mg./25 mg.) MYSTECLIN-F FOR SYRUP (125 mg./25 mg. per 5 cc.) MYSTECLIN-F FOR AQUEOUS DROPS (100 mg./20 mg. per cc.)

For complete information, consult package insert or write to Professional Service Department, Squibb, 745 Fifth Avenue, N. Y. 22, N. Y.

SQUIBB *Squibb Quality – the Priceless Ingredient*

NEW

MYSTECLIN-F

Squibb Phosphate-Potentiated Tetracycline (SUMYCIN) *plus* Amphotericin B (FUNGIZONE)

"MYSTECLIN"®, "SUMYCIN"® AND "FUNGIZONE"® ARE SQUIBB TRADEMARKS

now—two FILIBON formulas

for individualized pre- and postnatal support

two formulations—both phosphorus-free, both with noninhibitory intrinsic factor and well-tolerated iron—providing greater flexibility in meeting individual requirements in pregnancy and lactation.

you can recommend:
FILIBON® Capsules

Prenatal Supplement Lederle

Each capsule contains:

Vitamin A (acetate)	4,000 U.S.P. Units
Vitamin D	400 U.S.P. Units
Thiamine Mononitrate (B_1)	3 mg.
Pyridoxine (B_6)	1 mg.
Niacinamide	10 mg.
Riboflavin (B_2)	2 mg.
Vitamin B_{12} with AUTRINC® Intrinsic Factor Concentrate	½ N.F. Oral Unit
Ascorbic Acid (C) (as Calcium Ascorbate)	50 mg.
Vitamin K (Menadione)	0.5 mg.
Ferrous Fumarate (Elemental iron, 30 mg.)	91.2 mg.
Fluorine (as CaF_2)	0.015 mg.
Copper (as CuO)	0.15 mg.
Iodine (as KI)	0.01 mg.
Potassium (as K_2SO_4)	0.835 mg.
Manganese (as MnO_2)	0.05 mg.
Magnesium (as MgO)	0.15 mg.
Molybdenum (as $Na_2MoO_4.2H_2O$)	0.025 mg.
Zinc (as ZnO)	0.085 mg.
Calcium Carbonate	575 mg.

or you can prescribe:
FILIBON® F.A. Capsules

Prenatal Supplement with Folic Acid Lederle

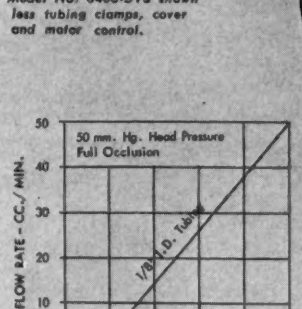
The complete FILIBON formula, *plus* 1 mg. of Folic Acid, essential for the prevention of the common megaloblastic anemias of pregnancy.

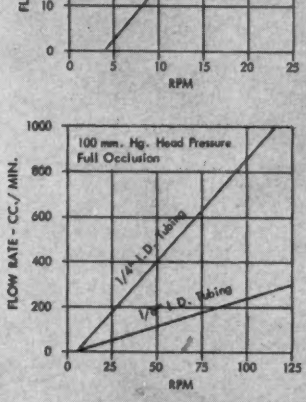
Lederle

LEDERLE LABORATORIES
A Division of
AMERICAN CYANAMID COMPANY
Pearl River, New York

NEW Low Flow Dual DeBakey Pump for perfusion and infusion

Model No. 3400-DVS shown less tubing clamps, cover and motor control.





This new low flow pump by MARK incorporates many outstanding design features. It provides dependability and versatility at a moderate price.

Condensed data

- Dependable control at flow rates less than 5cc/min. and greater than 1000cc/min.
- Dual pump head makes possible two flow rates simultaneously
- Occlusion setting by dial is instantaneous
- Variac controlled; quiet running
- Lightweight; portable

Write for complete brochure which includes flow charts for all sizes of tubing and various head pressures.

MARK

THE MARK COMPANY

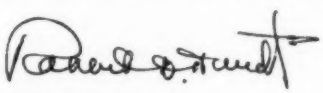
31 WEST STREET · RANDOLPH, MASS.

Armour Pharmaceutical Company extends its thanks to the profession

In the several months since the introduction of our new enteric-protected anti-inflammatory enzyme tablet, Chymoral, we have received some very encouraging comments from the profession regarding its clinical success in the enzymatic management of inflammatory processes. We would like to extend our thanks to those who have already used and commented on Chymoral. Since we are deeply interested in extending our knowledge of the therapeutic range of this new product, we will welcome any further comments you may want to make. To those who have not yet used Chymoral, we extend an offer to give it a therapeutic trial.

The therapeutic and prophylactic effects of Chymoral include anti-inflammatory, antiedematous and mucolytic activities.[1-6] It liquefies thick secretions in bronchitis and in asthma with bronchitis; eases the racking cough of emphysema and increases elimination of bronchial secretion; cuts healing time in accidental or surgical trauma; is a useful adjunctive therapy in inflammatory dermatoses; encourages healing in gynecologic conditions; reduces pain and swelling and thus promotes faster healing in urologic conditions; and reduces the extent of inflammatory changes in ophthalmic and otorhinolaryngic conditions.

We are very pleased indeed that the product has found a useful place in the range of therapeutic tools available to the doctor for management of the inflammatory process. Armour feels that enzymes are a new and exciting development in anti-inflammatory therapy; one which may well carry chemotherapeutics forward a long step.



Robert A. Hardt
President

1. Beck, C.; Levine, A. J.; Davis, O. F., and Horwitz, B.: Clinical Studies with an Oral Anti-inflammatory Enzyme Preparation. Clin. Med. 7:519, 1960. 2. Billow, B. W.; Cabodeville, A. M.; Stern, A.; Palm, A.; Robinson, M., and Paley, S. S.: Clinical Experience with an Oral Anti-inflammatory Enzyme for Intestinal Absorption. Southwestern Med. *41*:286, 1960. 3. Teitel, L. H.; Seigel, S. J.; Tendler, J.; Reiser, P., and Harris, S. B.: Clinical Observations with Chymotrypsin in 306 Patients. Indust. Med. & Surg. *29*:150, 1960. 4. Clinical Reports to the Medical Dept., Armour Pharmaceutical Company, 1959. 5. Reich, W. J., and Nechtow, M. J.: Scientific Exhibit, Chicago Medical Society (March) 1960. 6. Taub, S. J.: Paper presented Annual Meeting Pi Lambda Kappa Medical Fraternity, Miami, Florida (March) 1960.

ARMOUR PHARMACEUTICAL COMPANY • KANKAKEE, ILLINOIS
Armour Means Protection

©1960, A. P. Co.

for vaginal discharges!

NYLMERATE

NYLMERATE JELLY

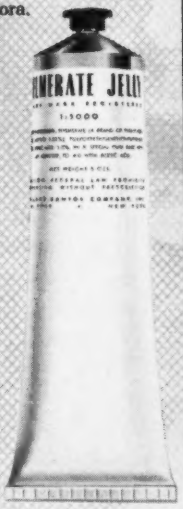
a proven effective agent in treating

TRICHOMONAS VAGINALIS VAGINITIS AND BACTERIAL VAGINITIS

Low surface tension allows for deep epithelial cell penetration. Kills most offending pathogens and re-establishes normal vaginal flora.

Prescribe: "Nylmerate Jelly with applicator"—5 oz. tube, also available in refill tube only. Simple to use . . . Applicator-full intravaginally morning and night preceded by a Nylmerate Solution water douche. Include treatment through menstrual period.

Available only on your prescription.



ACTIVE INGREDIENTS

Polyoxyethylenenonylphenol 0.10%
Phenylmercuric Acetate 0.02%
Boric Acid 1.0%
in a gum base with pH adjusted to 4

NYLMERATE SOLUTION CONCENTRATE

a therapeutic vaginal douche of choice

Excellent adjunct in the management of monilia and trichomonas vaginal infections. Restores normal vaginal flora through a 3-prong attack. Low surface tension aids in reaching the innermost recesses where organisms flourish. Unlike vinegar, affords a controlled pH of 4.1 in dilution and is effective in any vaginal pH. Broad range activity against protozoa—bacteria—and fungi. Well suited for office use in swabbing vaginal vault.

Available only on your prescription (eliminates excessive and unwarranted douching). Specify—Nylmerate Solution Concentrate pint bottle with measuring cap.

Prescribe two tablespoonfuls or one capful to two quarts of water twice daily. As a prophylactic, use once a day through two menses.

ACTIVE INGREDIENTS

Phenylmercuric Acetate 0.2% in a buffered solvent of Alcohol 50%, Acetone 10% and de-ionized water q.s., added certified color with pH adjusted to 4.9.

Literature available

HOLLAND-RANTOS CO., INC.
145 HUDSON STREET · NEW YORK 13, N.Y.

in induction and stimulation of labor—method of choice

PITOCIN

"Intravenous PITOCIN may be used successfully in elective or indicated inductions of labor. It has a definite place in the stimulation of labor in the early part or later stages either in desultory preliminary labor, or in primary or secondary uterine inertia."*

PITOCIN (oxytocin injection, Parke-Davis) is supplied in 0.5-cc. (5-unit) ampoules, in boxes of 10 and in 1-cc. (10-unit) ampoules, in boxes of 10. Each cc. contains 10 international oxytocic units (U.S.P. units).

PARKE-DAVIS

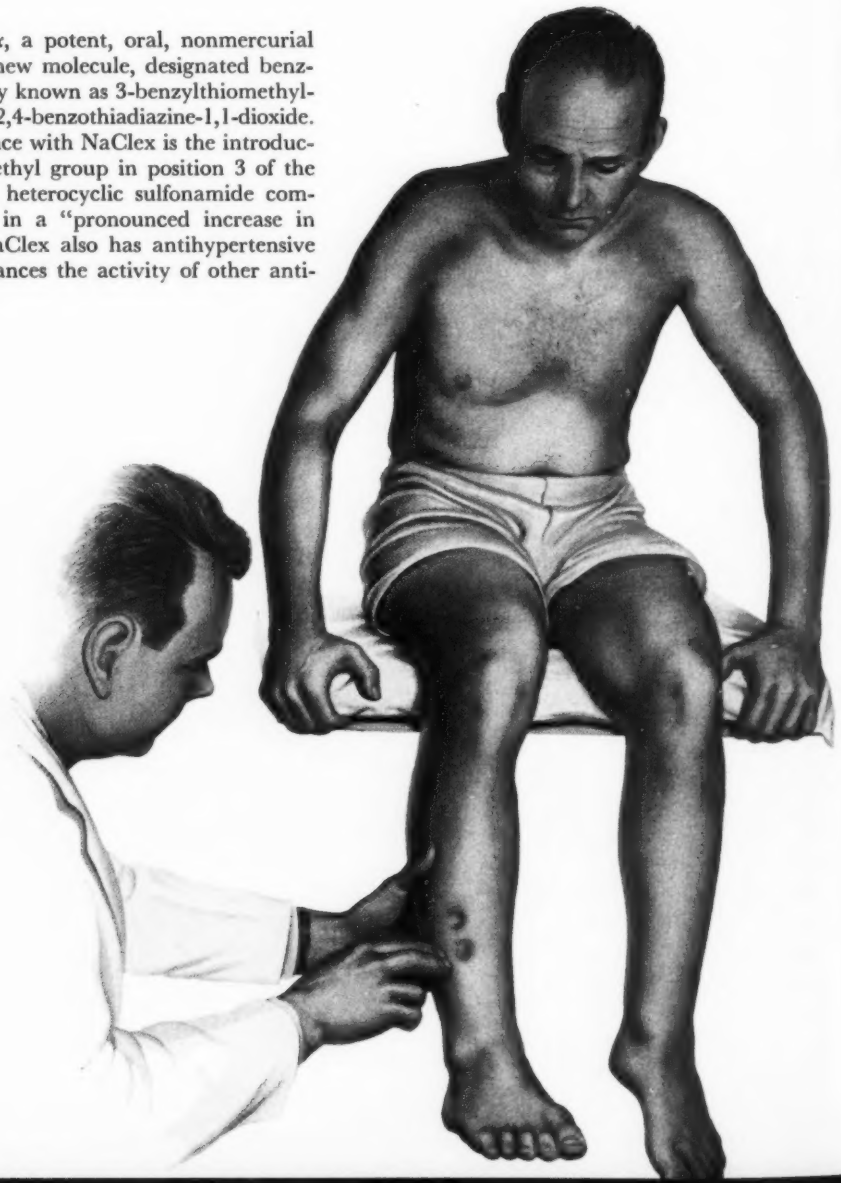
*Fields, H.; Greene, J. W., Jr., & Franklin, R. R.: *Obst. & Gynec.* 13:353, 1959. 33960 PARKE, DAVIS & COMPANY · Detroit 32, Michigan

benzthiazide

NaClex®

a new molecule with an unsurpassed faculty for salt excretion

Robins announces NaClex, a potent, oral, nonmercurial diuretic. NaClex is a new molecule, designated benzthiazide and chemically known as 3-benzylthiomethyl-6-chloro-7-sulfamyl-1, 2,4-benzothiadiazine-1,1-dioxide. The important difference with NaClex is the introduction of a benzylthiomethyl group in position 3 of the heterocyclic ring of a heterocyclic sulfonamide compound, which results in a "pronounced increase in diuretic potency."[1] NaClex also has antihypertensive properties, and it enhances the activity of other antihypertensive drugs.



in diuresis

salt removal is still the fundamental objective

As salt goes, so goes edema.

A fundamental principle of diuresis is that "increased urine volume and loss of body weight are proportional to and the osmotic consequences of loss of ions."[2] New NaClex helps reduce edema through the application of this basic principle.

Apparently functioning in the proximal renal tubules, NaClex strictly limits the reabsorption of sodium and chloride ions. To maintain the essential, subtle balance between salt and water, the body's homeostatic mechanism responds to this loss of ions by allowing an increased excretion of excessive extracellular water. Thus the NaClex-induced removal of salt leads directly to the reduction of edema.

How does NaClex benefit edematous patients?

Diuresis with NaClex provides an increase in the concentration of sodium and chloride in the urine as well as an increase in the total amount of salt and water removed. Furthermore, with NaClex, there is a relative sparing of potassium.

How potent is benzthiazide?

Compared tablet for tablet with the oral diuretics currently available, NaClex is unsurpassed in potency. On a mg. for mg. basis, NaClex has achieved optimum diuresis in pharmacologic animal studies at a dose one-twentieth that of chlorothiazide.

How soon and for how long does NaClex act?

Diuretic activity begins within two hours after the administration of NaClex and continues for twelve to eighteen hours. It reaches a peak from the fourth to sixth hours. In edematous patients given 50 mg. of NaClex daily for five days, maximum sodium excretion occurred during the first day and continued at this rate until excessive sodium stores were depleted.[1] Natriuresis then declined until it approximately balanced the sodium intake.

What are the major diuretic indications for NaClex?

NaClex produces marked diuresis, weight loss, and symptomatic improvement in edema associated with a wide variety of conditions such as congestive heart failure, cirrhosis of the liver, chronic renal diseases (including nephrosis), premenstrual tension, toxemia of pregnancy, and obesity. Edema of local origin and that caused by steroids may also benefit.

Is potassium or bicarbonate excretion a problem with NaClex?

In short-term therapy, excessive excretion of potassium is unlikely. In the effective dose range of NaClex, potassium loss varies from one-sixth to one-half that of sodium. Naturally, the ratio of these ions depends on the rate at which excess sodium stores are depleted, and whether the patient's salt intake is restricted.

At therapeutic levels, there is no appreciable increase in bicarbonate excretion.

Can NaClex and mercurials be given concurrently?

Yes, if desired. When they are employed concurrently, NaClex may increase the diuretic efficacy of mercurials. But NaClex alone is often effective enough to eliminate the need for parenteral mercurial administration. Also, NaClex may be effective in cases when mercurials are not.

A. H. ROBINS COMPANY, INC.

for more about NaClex, please turn page

benzthiazide

NaClex®

in hypertension effective alone or with other agents

To what extent is NaClex useful in hypertension?

NaClex has definite antihypertensive properties, and it may be used as the sole therapeutic agent in mild hypertension. In severer cases, NaClex may be used with other antihypertensive drugs. It potentiates their activity and permits their use at lower dosage. In hypertension with associated water retention, NaClex is of twofold value. It may be prescribed for congestive heart failure as an ancillary measure to digitalis.

Does NaClex affect normotensive patients?

NaClex does not lower the blood pressure of normotensive patients. But if they are edematous it still provides effective diuresis.

What are the recommended dosage schedules for NaClex?

In edema. A daily dosage of 50 mg. to 200 mg. should be used for several days or until maximum diuretic effect is achieved. When the dosage is more than 100 mg., it is usually best administered in two or more doses, e.g., after the morning and evening meals. Beneficial results may be maintained with 50 mg. to 150 mg. daily, depending on the patient's needs. The dosage should be reduced until the minimum effective dosage is reached.

In hypertension. Initial daily dosage: 50 to 100 mg., given in two doses of 25 mg. to 50 mg. after breakfast and lunch, and continued until a therapeutic drop in blood pressure is achieved. For maintenance, dosage should be adjusted according to the patient's response, either upward to as much as 50 mg. t.i.d. or downward to the minimum effective dosage. IMPORTANT: The dosage of therapeutic agents such as ganglionic blockers or hydralazine should be reduced by at least 50 per cent immediately upon adding NaClex to the regimen, in order to prevent excessive antihypertensive effects. Such a reduction becomes mandatory as a lower blood pressure is established under the potentiating effect of NaClex.

In premenstrual tension. Suggested initial daily dosage: 25 mg. to 50 mg., administered in one or two doses a day, starting with the onset of symptoms, or 5 to 7 days before the menstrual period, and continuing until the onset of menses.

In obesity. In obese patients in whom fluid retention is a complicating factor, 25 to 50 mg. may be administered once or twice a day to initiate a fluid loss.

Can dietary salt restrictions be eased with NaClex?

Because of the notable ability of NaClex to remove salt, consideration may be given to permitting a liberalization of the dietary salt intake for selected patients with edema or even some with hypertension or congestive heart failure. This easing of restrictions depends on the severity of each patient's disease and the probability of his following the prescribed regimen.

What if there is renal impairment?

As with all diuretics, if progressive renal impairment becomes evident, a careful reappraisal of therapy is necessary and consideration should be given to withholding or discontinuing diuretic therapy.

Do patients develop a tolerance for NaClex?

No. By virtue of its freedom from the development of tolerance, NaClex may often be employed over long periods with continuing effectiveness in the treatment of most patients with edema or hypertension.

Are any of the precautions for NaClex unusual?

No. In general, the precautions which apply to NaClex also apply to other thiazide diuretics. One important fact to remember is that diuretics do not correct the underlying mechanisms that produce edema although they may greatly improve the symptoms associated with it.

salt excretion still the basic objective in long-term diuretic therapy

What side effects may be expected?

Side effects to NaClex are infrequent and usually not severe. Most can be overcome by adjusting the electrolyte balance (by dietary supplementation), lowering the dose, or giving the drug after meals. Nausea, anorexia, and headache have been reported.

Reports on other thiazide diuretics have described reactions and responses such as decreased glucose tolerance (particularly in latent diabetes mellitus), hyperuricemia in untreated gout, leukopenia (neutropenia), purpura with or without thrombocytopenia and rash. With NaClex, rare instances of hyperuricemia, leukopenia, and rash have been reported.

Careful appraisal is always necessary to ascertain whether adverse symptoms and electrolyte disturbances are rising from therapy or from a progression of the underlying disease.

What about hypokalemia?

As mentioned before, with NaClex the excretion of potassium is relatively much less than that of sodium. In short-term therapy this loss is not excessive. When any diuretic is given for prolonged periods, of course, the patient should be observed regularly for early signs of hypokalemia. This is especially necessary in patients taking digitalis because of the possibility of digitalis toxicity.

Should a potassium deficiency occur, 2 to 5 Gm. of potassium chloride daily may be prescribed. Citrus fruits, bananas, or tomatoes may be substituted for the potassium chloride, if desired.

Patients with cirrhosis who are given NaClex continuously should be observed carefully for the development of impending hepatic coma and hypokalemia.

When NaClex is given to some patients with cirrhosis and ascites who are on a low dietary sodium intake, a profound loss of potassium through the urine may occur although the urine sodium may increase or remain unchanged. In such instances, serum potassium levels fall. All patients with cirrhosis and ascites who are given NaClex continuously should receive potassium supplements.

NOTE: the administration of corticosteroids may increase the loss of potassium.

Is hyponatremia or hypochloremic alkalosis likely with NaClex?

In a basic study of the repetitive effectiveness of benzthiazide, no significant changes in serum electrolytes were observed.[1] But, because the principal job of diuretics is to remove salt, it naturally follows that the patient should be observed regularly for early signs and symptoms of fluid or electrolyte imbalance. Hyponatremia and hypochloremic alkalosis are most likely to accompany vigorous diuretic therapy combined with rigid salt restriction. These complications can readily be corrected by appropriate electrolyte and fluid replacement.

Supply: NaClex is available in scored, yellow 50 mg. tablets, engraved "AHR."

References: 1. Ford, R. V., Cur. Therap. Res., 2:51, 1960. 2. Pitts, R. F., Am. J. Med., 24:745, 1958.

A. H. ROBINS COMPANY, INC.
RICHMOND 20, VA.

*"Experimental work and clinical observations to date indicate that this phenothiazine is . . . an effective antiemetic with exceedingly low toxicity, ..."**

MORNIDINE®

for better low-dosage control of postoperative vomiting

For postoperative vomiting, Mornidine (brand of pipamazine) is the most recent addition to the phenothiazines. It offers four important attributes for excellent postoperative control of vomiting:

1. low dosage
2. specific action on the vomiting center
3. remarkably low incidence of side effects – with greater safety
4. both tablet and parenteral forms

When Mornidine is combined with an analgesic the effective dose of the latter can be diminished. Further, there usually is a reduction in the uneasiness and anxiety of postoperative patients.

Mornidine comes in two dosage forms: tablets and ampuls for parenteral administration.

For complete information on the use of Mornidine in surgical patients refer to instructions enclosed with each ampul.

The usual adult dose is 5 mg. intramuscularly (1 cc.) or orally every four to six hours, as needed.

G. D. SEARLE & CO.
CHICAGO 80, ILLINOIS
Research in the Service of Medicine

*Friend, D. G.: Current Drug Therapy: The Phenothiazines, Clin. Pharm. & Therap. 1:5 (Jan.) 1960.

CARBOCAINE® hydrochloride

(Brand of mepivacaine hydrochloride)

a unique local anesthetic with "...outstanding features."[1]

Carbocaine combines the best characteristics of older local anesthetics with exceptional new advantages.

More potent
than procaine or lidocaine.[2]

•

Quicker onset of anesthesia
than obtained with other agents.[3]

•

More prolonged anesthesia
— lasts several hours.[1,4]

•

Greater safety
—low toxicity, virtually no vasodilatation,[1,3] epinephrine not required except for hemostasis.

•

Local anesthesia extended
to many more patients and procedures.[4,5]

•

Greater stability
—no risk of decomposition or loss of potency.

Carbocaine has been found suitable for elderly or poor risk patients, for patients with epilepsy or cardiac disease, as well as for many others in whom potent anesthetics are generally contraindicated.

For infiltration and nerve block, caudal and peridural block, and therapeutic block in management of pain.

How Supplied: For infiltration and nerve block: Carbocaine hydrochloride, 1 per cent and 2 per cent, in sterile saline solution, in multiple dose vials of 50 cc. For caudal and peridural block: Carbocaine hydrochloride, 1 per cent, in sterile modified Ringer's solution, in single dose vials of 30 cc.

References: 1. Sadove, M. S.: A preliminary report on Carbocaine, a new local anesthetic. Submitted for publication. 2. Luduena, F. P.; Hoppe, J. O.; Coulston, F., and Drobeck, H. P.: The pharmacology and toxicology of mepivacaine, a new local anesthetic, *Toxicol. & Appl. Pharmacol.* To be published. 3. Rovenstine, E. A.: Personal communication. 4. Young, J. A.: Upper arm block with Carbocaine (mepivacaine), a new anesthetic agent, *Anesth. & Analg.* To be published. 5. Griesser, Gerd: Erfahrungen mit einem neuen Lokalanestheticum, *Anaesthesist* 6:364, Oct., 1957.

Winthrop Laboratories
New York 18, N. Y.

Carbocaine (brand of mepivacaine), trademark reg. U. S. Pat. Off.

NEW
RADIOPAQUE PENROSE DRAINS
BY DAVOL

TWO major improvements that provide a greater sense of security for patient, hospital and physician:

1. **CENTIMETER CALIBRATION:** Permits rapid, accurate evaluation of the length of the indwelling portion of the Penrose Drain.

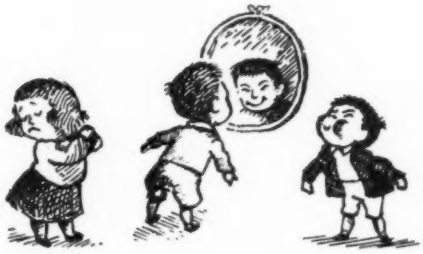
2. **RADIOPACITY:** Flat-plate radiographic examination discloses presence—or absence—of drain within a body cavity. Makes X-ray examination a simple method for determining retention of the drain within a cavity.

Research and development of the new radiopaque centimeter-calibrated Penrose Drains have been conducted in collaboration with: Dr. Donald F. McDonald, Chief of Urology, Strong Memorial Hospital; Professor of Urology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Dr. Walter J. Pories, Department of Surgery, Strong Memorial Hospital, Rochester, N. Y. Dr. Leonard H. Flax, Washington Hospital Center, Washington, D. C.

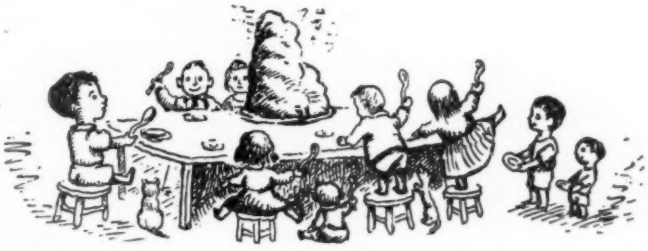
DAVOL RUBBER COMPANY
PROVIDENCE 2, R. I.

a mustache is to wear on Halloween

dogs are to kiss people



a face is something to have on the front of your head



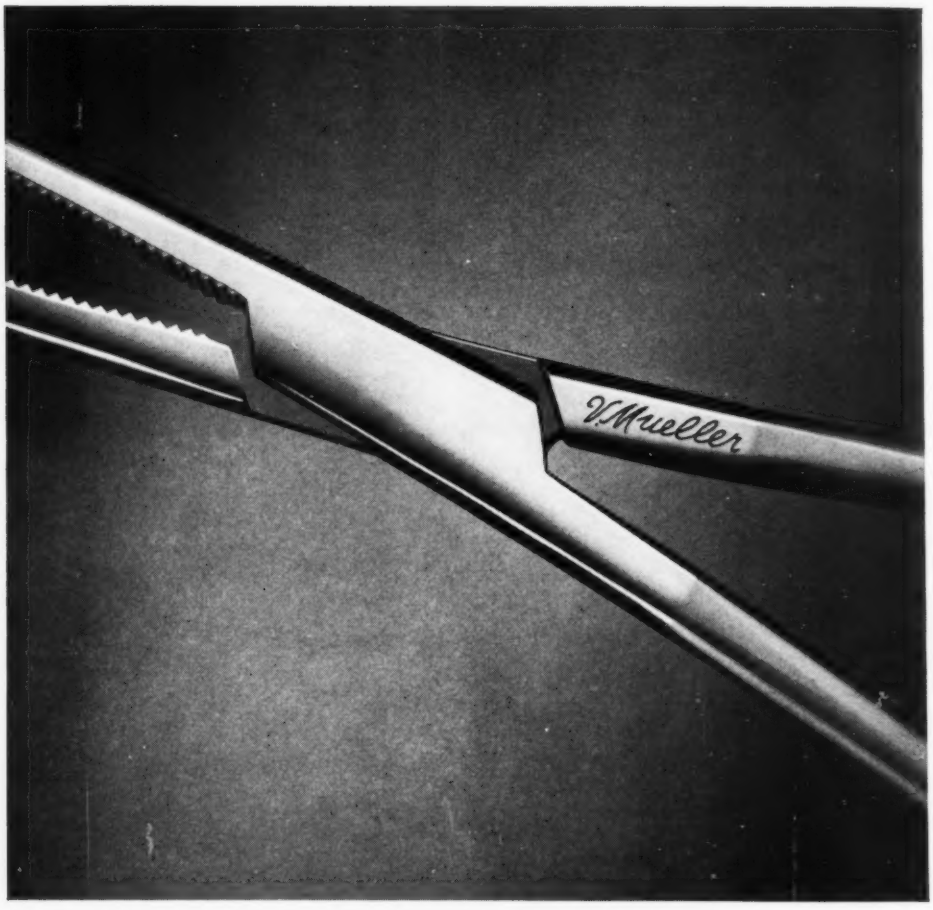
REDISOL® is so kids have better appetites

Redisol (Cyanocobalamin, crystalline vitamin B_{12}) often stimulates children's appetites with consequent weight gain.
Tiny **Redisol Tablets** (25, 50, 100, 250 mcg.) dissolve instantly in the mouth, on food or in liquids.
Also available: cherry-flavored **Redisol Elixir** (5 mcg. per 5-cc. teaspoonful); **Redisol Injectable,**
cyanocobalamin injection USP (30 and 100 mcg. per cc., 10-cc. vials and 1000 mcg. per cc. in 1, 5 and 10-cc. vials).

Drawings reproduced from "A Hole Is to Dig", copyright by Ruth Krauss and Maurice Sendak, published by Harper & Brothers.
For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

REDISOL IS A TRADEMARK OF MERCK & CO., INC.



to make the most of your talents and techniques . . .

A Most Significant "Signature" in Surgery

This famous "Signature" identifies every instrument in the superb *new line* of surgical forceps created by V. Mueller. The "Signature" line is made in limited supply expressly for the surgeon who seeks the same perfection in his instruments as he seeks in himself. This great new line compromises neither with quality nor with mass production economies. We will be pleased to send our "Signature" brochure at your request.

V MUELLER & CO.

Fine Surgical Instruments and Hospital Equipment Since 1895

330 S. Honore Street, Chicago 12, Illinois
Dallas • Houston • Los Angeles • Rochester, Minn.

confidence through experience

"Fluothane"—the most significant advance in inhalation anesthesia since the introduction of ether

NOW CONFIRMED IN HUNDREDS OF THOUSANDS OF CASES...OVER 200 PUBLISHED REPORTS TO DATE

"Fluothane" produces smooth, effective anesthesia . . . permits pleasant, rapid induction . . . allows rapid recovery and return to consciousness.

"Fluothane" does not increase bronchial, gastric, or salivary secretions. It minimizes capillary bleeding . . . causes minimal incidence of nausea and vomiting . . . and permits full use of electrocautery and x-ray during anesthesia because "Fluothane" is nonflammable, nonexplosive.

"FLUOTHANE"®

(BRAND OF HALOTHANE)

for precision inhalation anesthesia

Ayerst Laboratories • New York 16, N.Y. • Montreal, Canada

Ayerst Laboratories make "Fluothane" available in the United States by arrangement with Imperial Chemical Industries, Ltd.

5946

CAMP TRADE MARK *lumbosacral supports*

For Conservative Treatment of Low Back Conditions

A perfect solution to the style demands of the patient and the support demands of the physician. This girdle features a double hook and eye adjustment. It extends 4″ above the waistline to cover the lumbosacral region. Made of white cable net with a fabric front and back panel.

A support your male patient will wear. Made of natural, controlled-stretch elastic with two double elastic pull bands hooking into front tabs. Zipper front closing. Supplied with 4 shaped steels for more back support — extends 5″ above waist in back, only 2½″ in front.

In situations of low back pain or in cases of postoperative therapy, Camp's lumbosacral supports have a long history of providing protection and relief. Designed to immobilize, firm and rest the back from the dorsolumbar junction to an anchor point well down over the sacrum. These supports can be reinforced by steel uprights, the Camp spinal brace, or pads. Your authorized Camp dealer has many models (side lacing, back-lacing, no lacing) to select from in matching your specific needs. And basic types are made in a variety of fabrics to match the whims of your patient.

S. H. CAMP & COMPANY, JACKSON, MICHIGAN

CAMP

S. H. Camp & Company of Canada, Ltd., Trenton, Ontario

orally effective progestational therapy

NORLUTIN®

(norethindrone, Parke-Davis)

in conditions involving deficiency of progesterone . . .

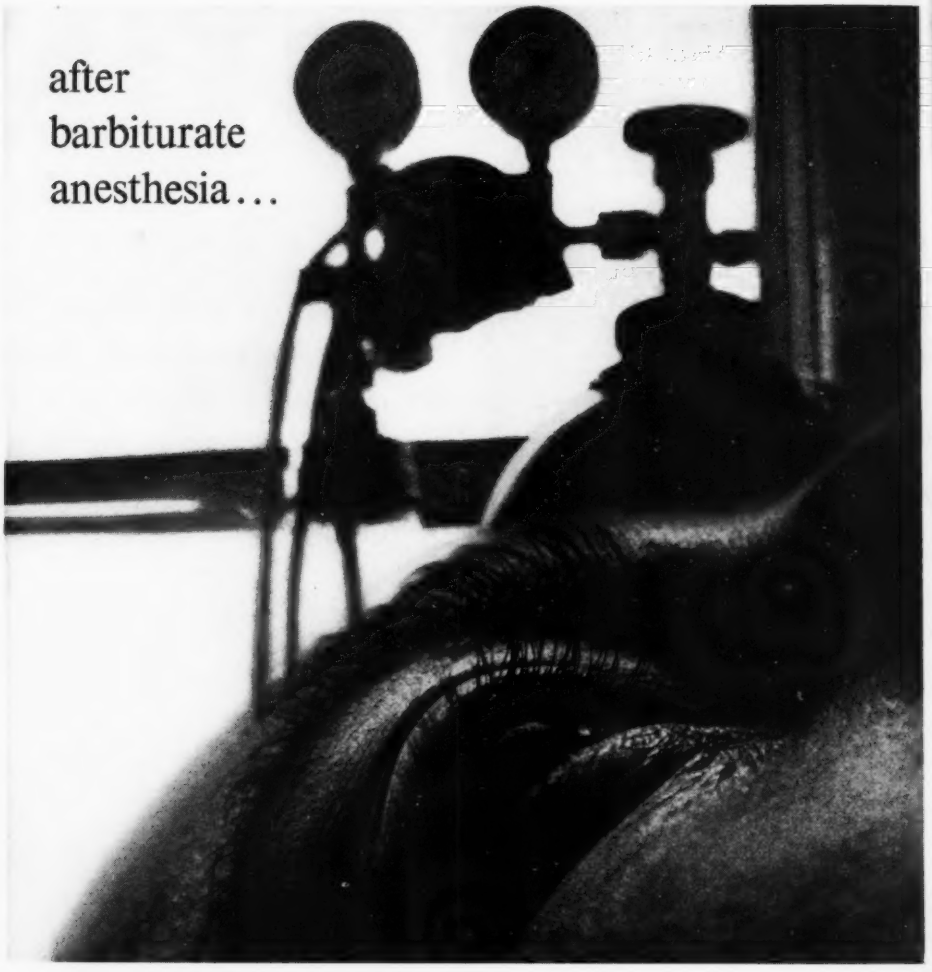
primary and secondary amenorrhea • menstrual irregularity • functional uterine bleeding • endocrine infertility • habitual abortion • threatened abortion • premenstrual tension • dysmenorrhea

PACKAGING: 5-mg. scored tablets, bottles of 30.

12660

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

PARKE-DAVIS



bring the patient into focus quicker

with **PARENTERAL RITALIN®**

An injection of parenteral Ritalin immediately after surgery "definitely accelerates wakefulness of patients anaesthetized . . . with intravenous barbiturates."[1] The optimum dose [of parenteral Ritalin] shortened recovery to about one-half that for the controls. . . ."[2] With rapid and smooth restoration of mental focus, postanesthetic depression is reduced and many postsurgical complications can be prevented. ■ Ritalin is also "effective in initiating respiration in patients after prolonged apnea due to central respiratory depression during anesthesia and in counteracting respiratory depression in the newborn."[3] *Complete information available on request.*

Supplied: PARENTERAL SOLUTION: *Multiple-dose Vials,* 10 ml., each vial containing 100 mg. Ritalin hydrochloride and 100 mg. lactose in lyophilized form.

References: 1. Percheson, P. B., Carroll, J. J., and Screech, G.: Canad. Anaesth. Soc. J. *6*:277 (July) 1959. 2. Gale, A. S.: Anesthesiology *19*:101 (Jan.-Feb.) 1958. 3. Gale, A. S.: Anesthesiology *19*:521 (July-Aug.) 1958.

CIBA
SUMMIT, NEW JERSEY

RITALIN® hydrochloride (methylphenidate hydrochloride CIBA)

ANNOUNCING—
SPECIFICALLY FOR
INFECTIONS DUE TO
"RESISTANT" STAPHYLOCOCCI

AN ENTIRELY NEW SYNTHETIC
"STAPH-CIDAL" PENICILLIN

Staphcillin™

sodium dimethoxyphenyl penicillin
FOR INJECTION

UNIQUE—BECAUSE IT
RETAINS ANTIBACTERIAL
ACTIVITY IN THE PRESENCE OF
STAPHYLOCOCCAL PENICILLINASE
WHICH INACTIVATES
OTHER PENICILLINS

Bristol™

STAPHCILLIN™

(sodium dimethoxyphenyl penicillin)

For Injection

DESCRIPTION

STAPHCILLIN is a unique new synthetic parenteral penicillin produced by Bristol Laboratories for the specific treatment of staphylococcal infections due to resistant organisms. Its uniqueness resides in its property of resisting inactivation by staphylococcal penicillinase. It is active against strains of staphylococci which are resistant to other penicillins.

Each dry filled vial contains: 1 Gm. STAPHCILLIN (sodium dimethoxyphenyl penicillin), equivalent to 900 mg. dimethoxyphenyl penicillin activity.

INDICATIONS

STAPHCILLIN is recommended as specific therapy only in infections due to strains of staphylococci resistant to other penicillins, e.g.:

Skin and soft tissue infections: cellulitis, wound infections, carbuncles, pyoderma, furunculosis, lymphangitis and lymphadenitis.

Respiratory infections: staphylococcal lobar or bronchopneumonia, and lung abscesses combined with indicated surgical treatment.

Other infections: staphylococcal septicemia, bacteremia, acute or subacute endocarditis, acute osteomyelitis and enterocolitis.

Infections due to penicillin-sensitive staphylococci, streptococci, pneumococci and gonococci should be treated with Syncillin® or parenteral penicillin G rather than STAPHCILLIN. Treponemal infections should be treated with parenteral penicillin G.

DOSAGE AND ADMINISTRATION

STAPHCILLIN is well tolerated when given by deep intragluteal or intravenous injection.

As is the case with other antibiotics, the duration of therapy should be determined by the clinical and bacteriological response of the patient. Therapy should be continued for at least 48 hours after the patient has become afebrile, asymptomatic and cultures are negative. The usual duration has been 5-7 days.

Intramuscular route: The usual adult dose is 1 Gm. every 4 or 6 hours. Infants' and children's dosage is 25 mg. per Kg. (approximately 12 mg. per pound) every 6 hours.

Intravenous route: 1 Gm. every 6 hours using 50 ml. of sterile saline solution at the rate of 10 ml. per minute.

**Warning:* Solutions of STAPHCILLIN and kanamycin should not be mixed, as they rapidly inactivate each other. Data on the results of mixing STAPHCILLIN with other antibiotics are being accumulated.

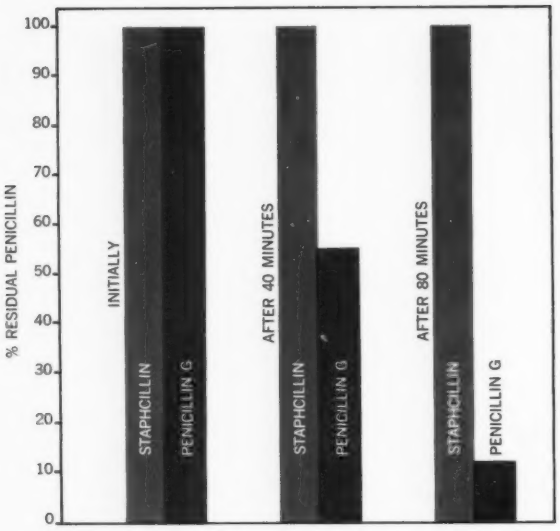
DIRECTIONS FOR RECONSTITUTION

Add 1.5 ml. sterile distilled water or normal saline to a 1 Gm. vial and shake vigorously. Withdraw the clear, reconstituted solution (2.0 ml.) into a syringe and inject. The reconstituted solution contains 500 mg. of STAPHCILLIN per ml. Reconstituted solutions are stable for 24 hours under refrigeration.

For intravenous use, dilute the reconstituted dose in 50 ml. of sterile saline and inject at the rate of 10 ml. per minute.

*This statement supersedes that in the Official Package Circulars dated September and/or October, 1960.

(continued)



In the presence of staphylococcal penicillinase, STAPHCILLIN remained active and retained its antibacterial action. By contrast, penicillin G was rapidly destroyed in the same period of time. *(After Gourevitch et al., to be published)*

Specifically for "resistant" staph...

Staphcillin™

sodium dimethoxyphenyl penicillin
FOR INJECTION

The failure of staphylococcal infections to respond to penicillin therapy is attributed to the penicillin-destroying enzyme, penicillinase, produced by the invading staphylococcus.

Unlike other penicillins:

1 STAPHCILLIN is effective because it retains its antibacterial activity despite the presence of staphylococcal penicillinase.

2 The clinical effectiveness of STAPHCILLIN has been confirmed by dramatic results in a wide variety of infections due to "resistant" staphylococci, many of which were serious and life-threatening.

Like other penicillins:

STAPHCILLIN has no significant systemic toxicity. It is well tolerated locally, and pain or irritation at the injection site is comparable to that following the injection of penicillin G. *In occasional cases, typical penicillin reactions may be experienced.*

PROFESSIONAL INFORMATION SERVICE – The attached Official Package Circular provides complete information on the indications, dosage, and precautions for the use of STAPHCILLIN. If you desire additional information concerning clinical experiences with STAPHCILLIN, the Medical Department of Bristol Laboratories is at your service. You may direct your inquiries via collect telephone call to New York, PLaza 7-7061, or by mail to Medical Department, Bristol Laboratories, 630 Fifth Ave., N. Y. 20, N. Y.

BRISTOL LABORATORIES • SYRACUSE, NEW YORK

Division of Bristol-Myers Company

CUT HERE FOR FILING

MICROBIOLOGICAL AND PHARMACOLOGICAL PROPERTIES

In vitro studies show that STAPHCILLIN is a bactericidal penicillin with activity against staphylococci resistant to penicillin G. Strains of staphylococci so far tested have been sensitive to STAPHCILLIN *in vitro* at concentrations of 1-6 mcg. per ml. These levels are readily attained in the blood and tissues by administration of STAPHCILLIN at the recommended dosage. This unique attribute is probably due to the fact that STAPHCILLIN is stable in the presence of staphylococcal penicillinase. STAPHCILLIN also resists degradation by *B. cereus* penicillinase. The antomicrobial spectrum of STAPHCILLIN with regard to other microorganisms is qualitatively similar to that of penicillin G; but considerably higher concentrations of STAPHCILLIN are required for bactericidal activity than is the case with penicillin G.

STAPHCILLIN is rapidly absorbed after intramuscular injection. Peak blood levels (6-10 mcg./ml. on the average after a 1.0 Gm. dose) are attained within 1 hour; and then progressively decline to less than 1 mcg. over a 4 to 6 hour period. It is poorly absorbed from the gastrointestinal tract. STAPHCILLIN is rapidly excreted by the kidney.

As shown by animal studies, STAPHCILLIN is readily distributed in body tissues after intramuscular injection. Of the tissues studied, highest concentrations are reached in the kidney, liver, heart and lung in that order; the spleen and muscles show lower concentrations of the antibiotic. STAPHCILLIN diffuses into human pleural and prostatic fluids, but its diffusion into the spinal fluid has not yet been completely studied. However, one patient with meningitis showed a significant concentration in his spinal fluid while on STAPHCILLIN therapy.

Toxicity studies with STAPHCILLIN and penicillin G in animals show that they have approximately the same low order of toxicity.

Certain staphylococci can be made resistant to STAPHCILLIN in the laboratory, but this resistance is not related to their penicillinase production. During the clinical trials, no STAPHCILLIN-resistant strains of staphylococci were observed or developed; the possibility of the emergence of such strains in the clinical setting awaits further observation.

PRECAUTIONS

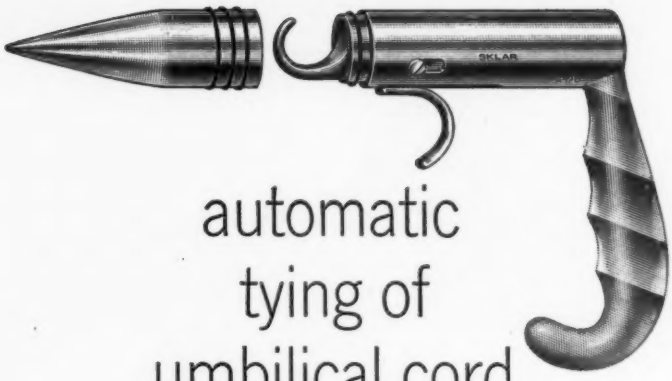
During the clinical trials, several mild skin reactions, e.g., itching, papular eruption and erythema were observed both during and after discontinuance of STAPHCILLIN therapy. Patients with histories of hay fever, asthma, urticaria and previous sensitivity to penicillin are more likely to react adversely to the penicillins. It is important that the possibility of penicillin anaphylaxis be kept in mind. Epinephrine and the usual adjuvants (antihistamines, corticosteroids) should be available for emergency treatment. Because of the resistance of STAPHCILLIN to destruction by penicillinase, parenteral *B. cereus* penicillinase may not be effective for the treatment of allergic reactions. Information with regard to cross-allergenicity between penicillin G, penicillin V, phenethicillin (Syncillin) and STAPHCILLIN is not available at present. If superinfection due to Gram-negative organisms or fungi occurs during STAPHCILLIN therapy, appropriate measures should be taken.

SUPPLY

List 79502 — 1.0 Gm. dry filled vial.

BRISTOL LABORATORIES · SYRACUSE, NEW YORK
Division of Bristol-Myers Company

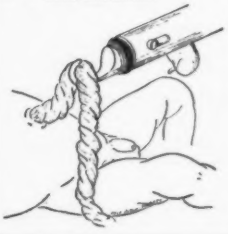
CUT HERE FOR FILING



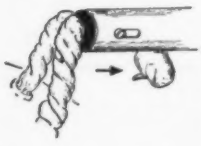
automatic tying of umbilical cord in 20 seconds with the GRAVLEE GUN*

by SKLAR

A Slack cord is looped over hook at desired distance from umbilicus.



B Trigger pull draws cord into barrel.

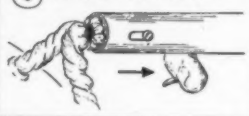


The Gravlee Gun provides a simple, positive, one-hand method for ligating umbilical cords of any size. Assures immediate and permanent hemostasis . . . prevents neonatal stump infections resulting from contaminated tapes or hands. Cords may be stripped if desired. The Gravlee Gun is sterilized by any of the conventional methods.[1]

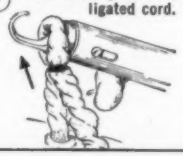
A SKLAR PRODUCT

Write for reprint and descriptive literature:
J. Sklar Manufacturing Co., Long Island City 4, N. Y.

C Additional pull slips sterile rubber band around cord.



D Release of trigger automatically delivers ligated cord.



E Cord is clamped distally and cut in the usual manner.

1. Gravlee, L. C., and Jones, W. N.: Obst. & Gynec. 15:43 (Jan.) 1960. * U. S. PAT. NO. 2,942,604.

Now...the only Nystatin combination with extra-active DECLOMYCIN®

Demethylchlortetracycline

with extra broad-spectrum benefits:—action at lower milligram intake... broad-range action... sustained peak activity... extra-day security against resurgence of primary infection or secondary invasion.

DECLOSTATIN®

Demethylchlortetracycline and Nystatin LEDERLE

CAPSULES, *150 mg. DECLOMYCIN Demethylchlortetracycline HCl and 250,000 units Nystatin.*

DOSAGE: *average adult, 1 capsule four times daily.*

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

Lederle

Stops the itch she dreads to scratch

IN PRURITUS VULVAE — whatever its cause — ES-A-CORT helps you control the intolerable itching and embarrassment within minutes. Clinical experience has proved ES-A-CORT's balanced combination of hydrocortisone, estrogen, and vitamin A . . . potentiated by DOME's exclusive ACID MANTLE vehicle . . . promptly and safely relieves inflammation, itching and edema; facilitates healing, and restores the normal tonicity, vitality and protective acidity of mucosa and skin.

ES-A-CORT™

CREME (pH 4.6) **LOTION**

micronized hydrocortisone alcohol, vitamin A and estrone in the exclusive ACID MANTLE® vehicle.

DOME CHEMICALS INC.

New York Los Angeles

DOME

WORLD LEADER IN DERMATOLOGICALS

another patient with hypertension?

indicated in all degrees of hypertension

effective by itself in most hypertensives

HYDROPRES*

HYDRODIURIL® (HYDROCHLOROTHIAZIDE) with RESERPINE

HYDROPRES can be used:

- *alone* (In most patients, HYDROPRES is the only antihypertensive medication needed.)
- *as basic therapy, adding other drugs if necessary* (Should other antihypertensive agents need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.)
- *as replacement therapy, in patients now treated with other drugs*
  (In patients treated with rauwolfia or its derivatives, HYDROPRES can produce a greater antihypertensive effect. Moreover, HYDROPRES is less likely to cause side effects characteristic of rauwolfia, since the required dosage of reserpine is usually less when given in combination with HydroDIURIL than when given alone.)

HYDROPRES-25
25 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one to four times a day.

HYDROPRES-50
50 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one or two times a day.

also available: **HYDROPRES-Ka-50**
50 mg. HydroDIURIL, 0.125 mg. reserpine, 572 mg. potassium chloride.
One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

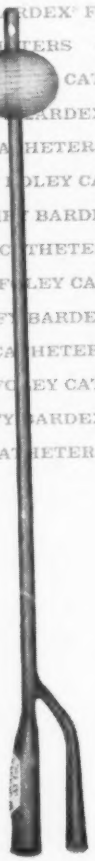
For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

*HYDROPRES, HYDROPRES-Ka, AND HYDRODIURIL ARE TRADEMARKS OF MERCK & CO., INC.

ECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY
TERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS
ARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDE
PECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIF
ETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETER
BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDE
ECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY
TERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS
ARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDE
CIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY
TERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS
ARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX
SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECI
HETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETE
BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARI
SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPEC
THETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETE
Y BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BAR
SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECI
HETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETE
BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARI
PECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIF
IETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETER
BARDEX® FOLEY CATHETERS • SPECIFY BARDEX® FOLEY CATHETERS • SPECIFY BARD

day after day, year after year . . .
to ensure dependable performance,
hospitals continue to specify
more Bardex® Foley Catheters
than all other brands combined



QUALITY INTEGRITY SERVICE
BARD
SINCE 1907

C. R. BARD, INC. Summit, New Jersey

metabolic support in the "therapeutic" jar

Homeostasis is a key factor in uneventful and rapid postoperative convalescence . . . and STRESSCAPS can help promote homeostasis. Nutritional support is essential.[1-3] High potency B and C vitamins form the basis for metabolic regeneration of affected tissues and offset usual stress depletion from other organs and tissues of the body.[3] The decorative jar is therapeutically important for the home-bound patient . . . it provides a convenient reminder of daily dosage essential to normal recovery.

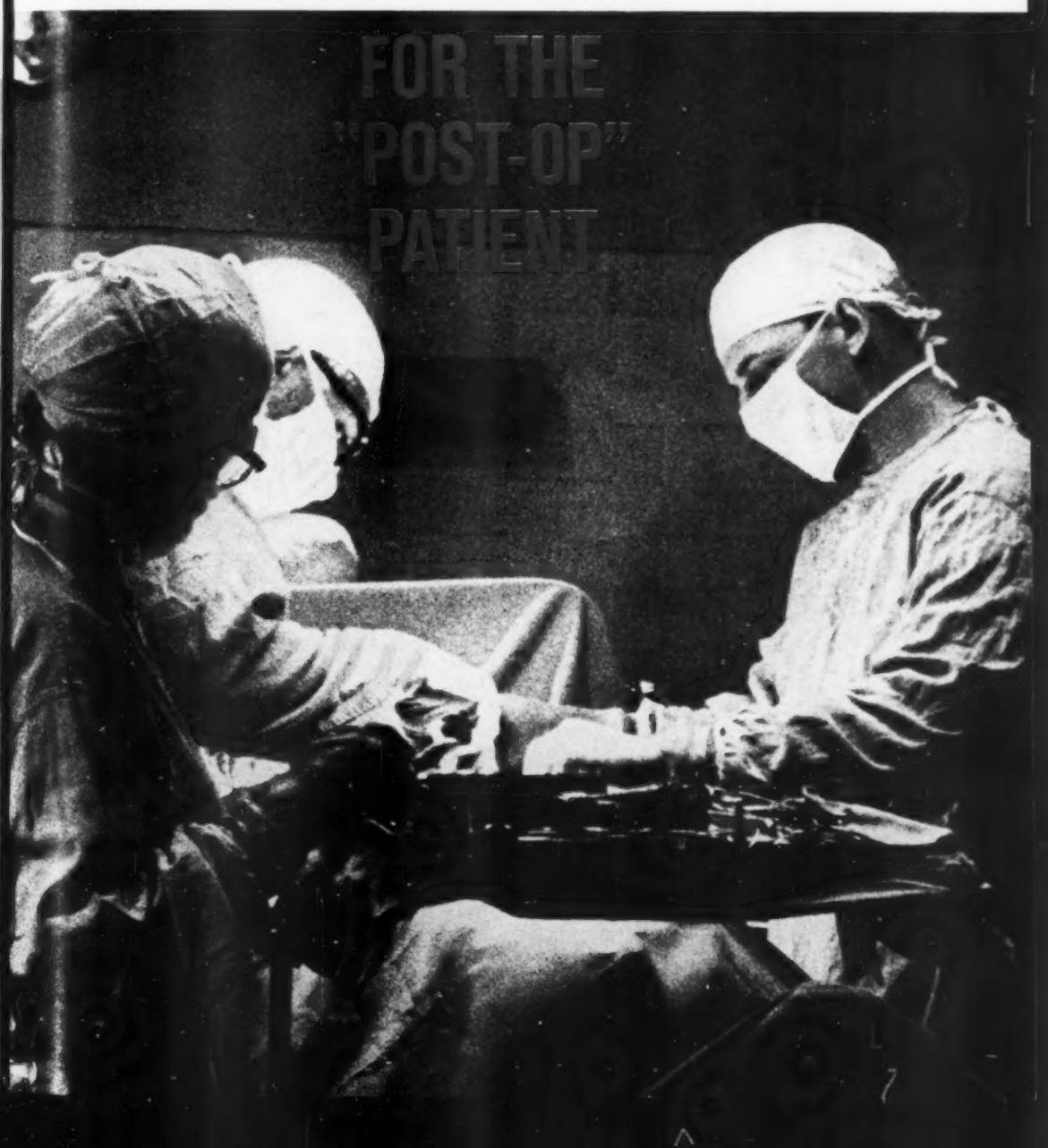
Each capsule contains: Thiamine Mononitrate (B_1) 10 mg., Riboflavin (B_2) 10 mg., Niacinamide 100 mg., Ascorbic Acid (C) 300 mg., Pyridoxine HCl (B_6) 2 mg., Vitamin B_{12} 4 mcgm., Calcium Pantothenate 20 mg., Vitamin K (Menadione) 2 mg. Average dose: 1-2 capsules daily.

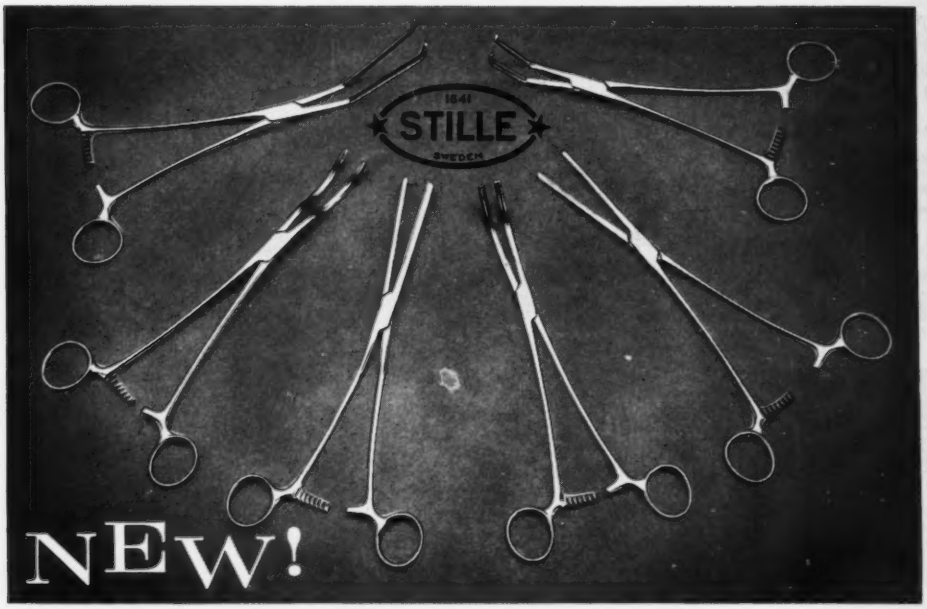
1. Priest, J. T.: Surg., Gynec. & Obstet. 107:375 (Sept.) 1958. 2. Kreiger, H., et al.: Surgery 44:138 (July) 1958. 3. Goodhart, R. . : M. Clin. North America 40:1473 (Sept.) 1958.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

STRESSCAPS®

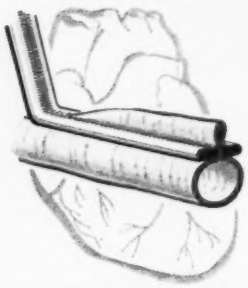
Stress Formula Vitamins Lederle





atraumatic CARDIOVASCULAR CLAMPS

by Senning-Stille



Clamps shown above, left to right:

Model 43-69 — Satinsky style, for aneurisms, etc., straight section of jaw 5.5 cm. (Large)

Model 43-74 — Spoon-type jaw for anastomosis, etc.

Model 43-71 — Angulated for coarctation, etc.

Model 43-73 — Curved jaw for anastomosis, etc.

Model 43-70 — Straight for coarctation, etc.

Model 43-68 — Satinsky style, for aneurisms, etc., straight section of jaw 3. cm. (Small)

New from Sweden! Senning-Stille Cardiovascular Clamps feature a unique jaw design that prevents slipping and greatly reduces the danger of cutting and tearing. Because there is a smooth rounded section behind the teeth, these clamps *grip* rather than *crimp*. This design minimizes the danger of puncturing the intima or crushing the adjacent tissue. The teeth are also set slightly outward. Thus, once applied, any increase in intraluminal pressure will result in a still firmer grip.

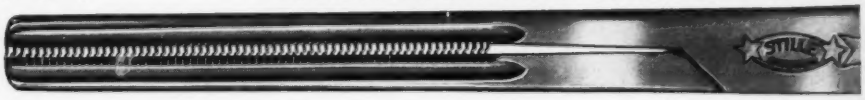
Although these clamps were originally designed for cardiovascular procedures, many clinics are now using them in bowel and anastomosis work due to their gentle non-crushing characteristics.

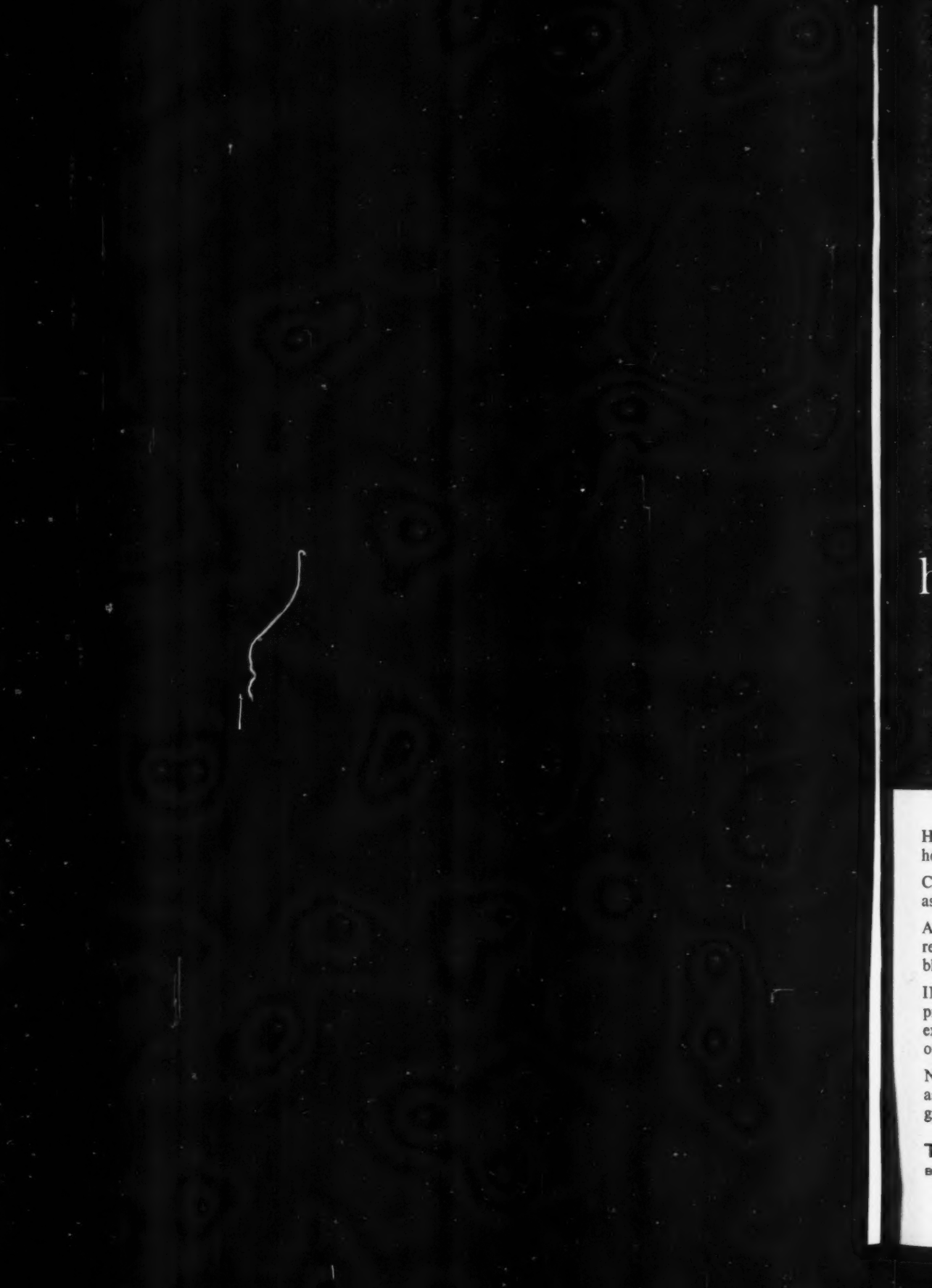
For further information on Stille instruments please write: Dept. SGO- 12, Ohio Chemical & Surgical Equipment Co., Madison 10, Wis. **On West Coast:** Ohio Chemical Pacific Co., Berkeley 10, Calif. (Divisions of Air Reduction Company, Incorporated)

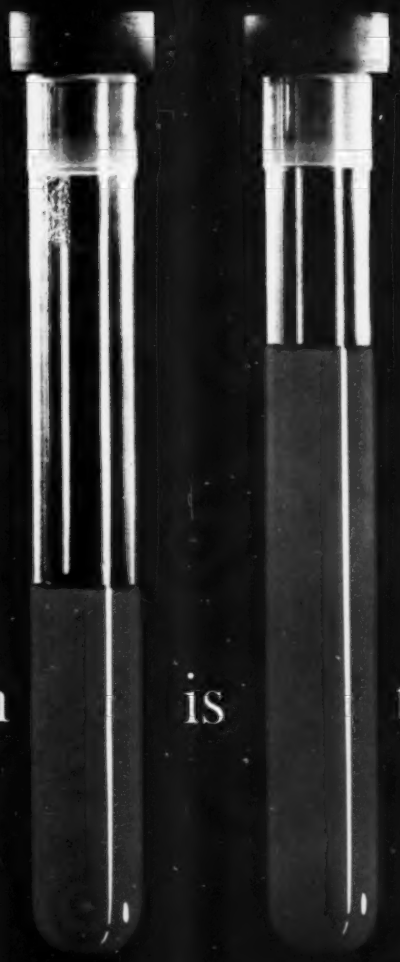
Sole Distributor in the U.S.A.

OHIO® Ohio Chemical

SERVING THE MEDICAL PROFESSION FOR FIFTY YEARS 1910-1960







how much is too much?

How much blood loss a patient can withstand depends on many factors. However, the wisdom of holding blood loss to a minimum is generally accepted.

Clinical studies show increased capillary permeability and fragility cause abnormal bleeding four times as often as do coagulative and other intravascular defects.[1,2]

Adrenosem decreases capillary permeability and promotes the retraction of severed capillary ends by restoring normal tone to capillary walls. Thus Adrenosem controls the primary cause of abnormal bleeding.

IN SURGERY . . . Administered preoperatively, Adrenosem protects against excessive bleeding from small vessels, adding extra safety and providing a clearer operative field. Postoperatively, Adrenosem reduces seepage and oozing.

NON-SURGICAL . . . Adrenosem controls internal bleeding associated with vascular pathosis, as in peptic ulcer, telangiectasia, purpura, ecchymosis, ulcerative colitis, and others.

1. Haden, R.L., Schneider, R.H., and Underwood, L.C.: Ann. N.Y. Acad. Sc., 49:641 (May 11, 1948).
2. Cheraskin, E.: J. Am. Dent. Assn., 58:17 (Apr., 1959).

Adrenosem®*

SALICYLATE

(Brand of carbazochrome salicylate)

*U. S. Pat. Nos. 2581850, 2506294

THE S. E. MASSENGILL COMPANY

BRISTOL, TENN. • NEW YORK • KANSAS CITY • SAN FRANCISCO

Adrenosem®

SALICYLATE (Brand of carbazochrome salicylate)

for safe, effective hemostasis... proven by 30 published clinical studies*

Over six years of clinical use and millions of doses prove the effectiveness and safety of Adrenosem. At recommended dosage levels there are no contraindications.

Supplied:

Ampuls	5 mg., 1 cc.: packages of 5 and 100 10 mg., 2 cc.: packages of 5
Tablets	1 mg. (s.c. orange): bottles of 50 2.5 mg., (s.c. yellow): bottles of 50
Syrup	2.5 mg. to each 5 cc. (1 teaspoonful): 4-oz. bottles

Potency of all dosage forms is stated in terms of the active ingredient, adrenochrome monosemicarbazone.

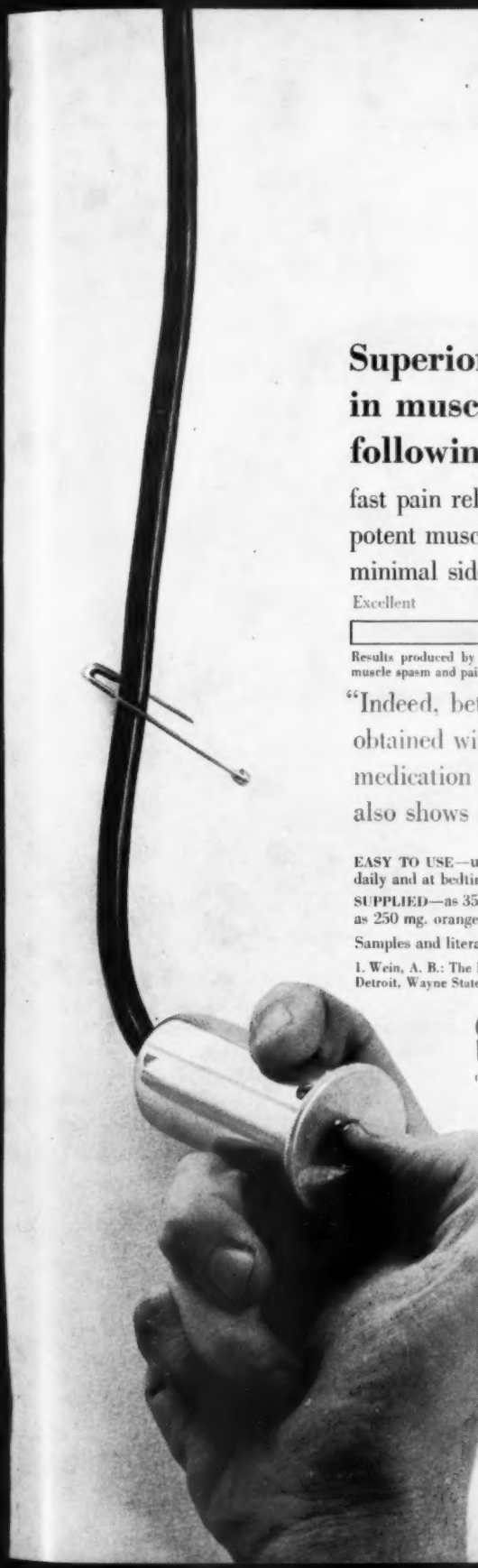
A detailed brochure is available on request.

*Bibliography:

1. Derouaux, G., and Roskam, J.: Adrenaline, Adrenalone, and Mean Bleeding Time, J. Physiol. 90:65 (1937).
2. Roskam, J.: Arrest of Bleeding, Charles C Thomas, Springfield, Ill. (1954).
3. Peele, J.C.: Adrenosem in the Control of Hemorrhage from the Nose and Throat, A.M.A. Arch. of Otolaryng. 61:450 (Apr., 1955).
4. Fulton, G.P., Lutz, B.R., Shulman, M.H., and Arendt, K.A.: Moccasin Venom as a Test for Susceptibility to Petechial Formation in the Hamster. Venoms: Published by the Am. Assoc. for the Advancement of Science (1954).
5. Pappenheimer, J.R.: Passage of Molecules Through Capillary Walls, Physiol. Rev. 33:387 (July, 1953).
6. Bacala, J.C.: The Use of the Systemic Hemostat Carbazochrome Salicylate, West. J. Surg., Obstet., and Gynec. 64:86 (Jan., 1956).
7. Kingsbury, B.C., Jr., and Young, H.E.: A Preliminary Report on Adrenosem Salicylate for Control of Hemorrhage, J. Calif. State Dental Assn. and Nev. State Dental Assn. 31:163 (May-June, 1955).
8. Moss, A.A.: Control of Hemorrhage in Dental Surgery, Dental Survey 32:1622 (Dec., 1956).
9. Ryan, Allan J.: Control of Bleeding in Familial Telangiectasia, The Meriden Hosp. Bull. 7: (Jan., 1958).
10. Peele, J.C.: Further Observations on the Use of Adrenosem Salicylate in the Control of Hemorrhage from the Nose and Throat, N. Car. Med. J. 17:98 (Mar., 1956).
11. Peele, J.C.: Control of Hemorrhage from the Nose and Throat, Med. Times 86:1228 (Oct., 1958).
12. Brode, H.A., and Chianese, T.C.: A Clinical Evaluation of Adrenosem Salicylate, Ann. of Dentistry 15:56 (Sept., 1956).
13. Owings, Capers B.: The Control of Postoperative Bleeding with Adrenosem, Laryngoscope 65:21 (Jan., 1955).
14. Perkins, R.E.L.: A Clinical Investigation of Adrenochrome Monosemicarbazone Sodium Salicylate, Oral Surg., Oral Med., Oral Path. 10:230 (Mar., 1957).
15. Zubieta, C.B., and Escanaverino, R.B.: Adrenosem for the Prevention of Bleeding in Tonsillectomy, Am. Pract. & Dig. of Treatment 8:385 (Mar., 1957).
16. Orzac, E.: Medical Care of the Child Patient Before and After Adenoidectomy and Tonsillectomy, N.Y. State J. Med. 56:886 (Mar., 1956).
17. Riddle, A.C., Jr.: Adrenosem Salicylate: A Systemic Hemostatic, Oral Surg., Oral Med., Oral Path. 8:617 (June, 1955).
18. Roberts, E.W.: Observations on the Use of Adrenochrome in Dental Practice, Oral Surg., Oral Med., Oral Path. 10:52 (Jan, 1957).
19. Brown, W.S.: Control of Bleeding After Dermabrasion, Northwest Med. 57:470 (Apr., 1958).
20. Dimmette, J.E., and Terry, J.G.: Better Control of Bleeding in Vaginal Hysterectomy, presented before the Texas State Med. Society, Surgical Section (Jan., 1956).
21. Sherber, D.A.: The Control of Bleeding, Am. J. Surg. 86:331 (Sept., 1953).
22. Dennehy, P.J.: The Care of the Prostatic Cavity, S. African Med. J. 30:381 (Apr., 1956).
23. Ersner, M.S., and Lerner, S.S.: The Unsolved Problem of the Tonsils and Adenoids, The Med. Clinics of N. Amer. 40:1749 (Nov., 1956).
24. Rasi, H.B.: Minimizing Postoperative Ecchymosis, The Am. J. of Surgery 96:751 (Dec., 1958).
25. Coyle, J.E.: Analysis of Blood and Vascular Factors in the Prophylaxis of Tonsillo-Adenoidal Hemorrhage, Laryngoscope 10:1029 (Oct., 1957).
26. Proctor, D.F., and Douglass, C.C.: Bleeding Following Tonsil and Adenoid Operations, Trans. Amer. Acad. Ophthal. Otolaryngol. 62:592 (July-Aug., 1958).
27. Bourgoyne, J.R.: Adrenosem and the Bleeder (In press)
28. Nicely, P., F.A.C.S., F.I.C.S. (Personal communication).
29. Wilkins, B.D.: Gastrointestinal Bleeding as Seen by the Proctologist, J.A.M.A. 163:1214 (April. 6, 1957).
30. Feinblatt, T.M., Feinblatt, H.M., and Ferguson, E.A.: Successful Non-Surgical Uses of Carbazochrome Salicylate, Amer. Pract. & Dig. of Treatment, 9:1827 (Nov., 1958).
31. Stich, M.H.: Carbazochrome Salicylate Therapy in Hereditary Hemorrhagic Telangiectasia, N.Y. State J. of Med., 59:2725 (July 15, 1959).

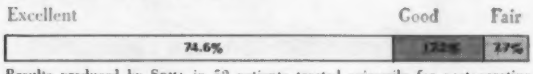
THE S. E. MASSENGILL COMPANY, Bristol, Tennessee • New York • Kansas City • San Francisco

dies*



Superior results in muscle spasm and pain following surgery

fast pain relief
potent muscle relaxation
minimal side effects



Results produced by SOMA in 52 patients treated primarily for postoperative muscle spasm and pain.[1]

"Indeed, better muscle relaxation has been obtained with it [SOMA] than with any other medication which I have used so far and it also shows an ability to relieve pain."[1]

EASY TO USE—usual adult dose is one 350 mg. tablet three times daily and at bedtime.

SUPPLIED—as 350 mg. white tablets, bottles of 50; for pediatric use, as 250 mg. orange capsules, bottles of 50.

Samples and literature on request.

1. Wein, A. B.: The Pharmacology and Clinical Usefulness of Carisoprodol. Detroit, Wayne State University Press, 1959, p. 156.

SOMA®

[carisoprodol Wallace]

WALLACE LABORATORIES / Cranbury, N. J.

For the care of dry, sensitive skin
pleasingly and efficiently serving
patient and physician during all seasons

Superfatted

BASIS® SOAP

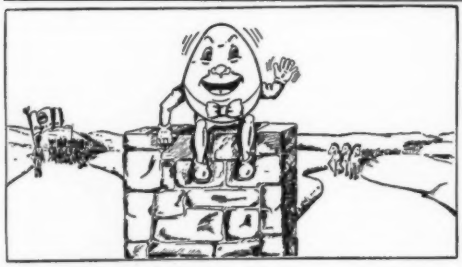
and

NIVEA® SKIN OIL

the surgeon's hand lotion

DUKE LABORATORIES, INC.
SOUTH NORWALK, CONN., U. S. A.

Manufacturers of Elastoplast® the original elastic adhesive bandage



HUMPTY DUMPTY SAT ON A WALL
HUMPTY DUMPTY HAD A GREAT FALL,
ALL THE KING'S HORSES AND ALL THE KING'S MEN
COULDN'T PUT HUMPTY DUMPTY TOGETHER AGAIN.
BECAUSE—IN THAT DAY THEY DID NOT HAVE

The RUSH MEDULLARY PIN

anorectic-ataractic ®

BAMADEX

meprobamate 400 mg., with d-amphetamine sulfate 5 mg., Tablets

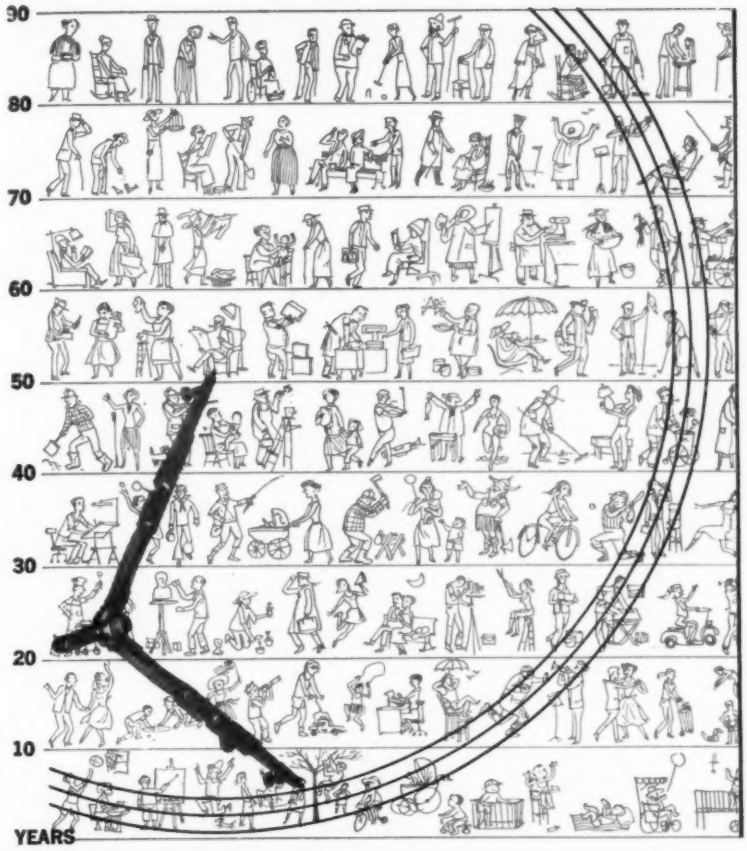
FOR THERAPY
OF OVERWEIGHT PATIENTS

- d-amphetamine depresses appetite and elevates mood
- meprobamate eases tensions of dieting (yet without overstimulation, insomnia or barbiturate hangover).

Dosage: One tablet one-half to one hour before each meal.

A LOGICAL COMBINATION
IN
APPETITE CONTROL

Ladarle



ATARAX ENCOMPASSES MORE PATIENT NEEDS...LETS YOU CHART A SAFER, MORE EFFECTIVE COURSE TO TRANQUILITY

ATARAX has a wide range of flexibility . . . from mild adult tensions and anxieties to full-blown alcoholic episodes . . . from the behavior disorders of childhood to the emotional problems of old age. Why? Because it gives you maximum adaptability of dosage . . . works quickly and predictably . . . is unsurpassed in safety.

ATARAX offers extra pharmacologic actions especially useful in certain troublesome conditions. It is antihistaminic and mildly antiarrhythmic, does not stimulate gastric secretions. Hence it is well suited to the needs of your allergic, cardiac and ulcer patients.

Have you discovered all the benefits of ATARAX?

Dosage: Adults, one 25 mg. tablet, or one tbsp. Syrup q.i.d. Children, 3-6 years, one 10 mg. tablet or one tsp. Syrup t.i.d.; over 6 years, two 10 mg. tablets or two tsp. Syrup t.i.d.

Supplied: Tiny 10 mg., 25 mg., and 100 mg. tablets, bottles of 100. Syrup, pint bottles. Parenteral Solution: 25 mg./cc. in 10 cc. multiple-dose vials; 50 mg./cc. in 2 cc. ampules. Prescription only.

Complete bibliography available on request.

ATARAX®

(BRAND OF HYDROXYZINE)

PASSPORT TO TRANQUILITY

Roerig

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being™

VITERRA® for vitamin-mineral supplementation
- capsules • tastitabs®
- therapeutic capsules

Three major criteria for an effective laxative have been established by physicians*

1. freedom from griping or other irritating side effects

2. clinically proven effectiveness

3. predictable action

*Results of a survey of over 1,000 physicians conducted by the Bureau of Research, Inc., 555 W. Jackson Blvd., Chicago 6, Illinois (April, 1960).

PERI-COLACE®

Anthraquinone derivatives from cascara and dioctyl sodium sulfosuccinate, Mead Johnson

meets physicians' criteria for an effective laxative

With Peri-Colace "...side effects such as griping are reduced to a minimum."[1]

Peri-Colace, a unique combination of Peristim® and Colace® (dioctyl sodium sulfosuccinate) "...gave satisfactory results in 97 per cent of the cases [130 hospitalized patients]."[2]

Experience in practice has shown the unusual dependability of Peri-Colace.[1-4] It promptly, yet gently, induces bowel evacuation within 8 to 12 hours in most patients.

References: (1) Broders, A. C., Jr.: Am. J. Digest. Dis. *2*:483-486 (Sept.) 1957. (2) Lamphier, T. A.: Am. J. Proctol. *8*:442-444 (Dec.) 1957. (3) Smigel, J. O.; Lowe, K. J.; Hosp, P. H., and Gibson, J. H.: M. Times *86*:1521-1526 (Dec.) 1958. (4) Turell, R.: Curr. M. Dig. *26*:61-69 (Feb.) 1959.

Mead Johnson

Symbol of service in medicine

35160

ILOPAN®

to prevent...to relieve... post-op distention and ileus

Surgical stress appears to increase the body's pantothenic acid requirements. ILOPAN (d-pantothenyl alcohol, W-T) provides additional pantothenic acid to aid restoration of normal peristalsis. Clinical studies and hundreds of case histories[1, 2] attest the effectiveness of ILOPAN against postoperative retention of flatus and feces — even paralytic ileus — and in reducing the need for intestinal intubation, or the period of intubation.

ILOPAN may be used with a high degree of safety — is not contraindicated even under conditions of mechanical bowel obstructions, produces no hyper-peristalsis or cramping, no side effects — and can be routinely administered by the nurse.

Supplied in:
1 cc. AMPULS (250 mg.)
2 cc. AMPULS (500 mg.)
10 cc. VIALS (2500 mg.)

1. Kareha, L. G., de Quevedo, N. G., Tighe, P., Kehrli, H. J., "Evaluation of Ilopan in Postoperative Abdominal Distention," Western J. Surg. Obs. & Gyn., 66:220, 1958.
2. Stone, M. L., Schlussel, S., Silberman, E., Mersheimer, W. L., "The Prophylaxis and Treatment of Postpartum and Postoperative Ileus with Pantothenyl Alcohol," Amer. J. Surgery, 97:191, 1959.

THE WARREN-TEED PRODUCTS COMPANY
COLUMBUS 8, OHIO
Dallas Chattanooga Los Angeles Portland

WARREN-TEED PHARMACEUTICALS

Helps you take the misery out of menopause

as hormones alone often don't do

Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Dosage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).

Supplied: **Milprem-400**, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). **Milprem-200**, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

Literature and samples on request.

Milprem®

(Miltown® plus natural estrogens)

EMP-1306

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

WALLACE LABORATORIES / *Cranbury, N. J.*

What does high "ABA" mean to you?

High serum levels of antibacterial activity mean fewer treatment failures in severe infections or in infections only marginally sensitive to penicillin. In other words, high "ABA" means . . .

consistently dependable clinical results

V-CILLIN K®

(penicillin V potassium, Lilly)

intense antibacterial activity

V-Cillin K produces greater antibacterial activity in the serum against the common pathogens than any other oral penicillin.[1-3]

unsurpassed safety

No form of penicillin has been shown to be less allergenic or less toxic than V-Cillin K.[4,5]

proved clinical effectiveness

Documented experience with penicillin V and potassium penicillin V reveals the clinical excellence of V-Cillin K.

ELI LILLY AND COMPANY
INDIANAPOLIS 6, INDIANA, U.S.A.

053004

Now at lower cost to your patient

Prescribe V-Cillin K, in scored tablets of 125 and 250 mg., or V-Cillin K, Pediatric, in 40 and 80-cc. bottles.

References

1. McCarthy, C. G., and Finland, M.: Absorption and Excretion of Four Penicillins, New England J. Med., *263*:315 (August 18), 1960. 2. McCarthy, C. G., Hirsch, H. A., and Finland, M.: Serum Levels after Single Oral Doses of 6-(a-phenoxypropionamido) Penicillanate and Penicillin V, Proc. Soc. Exper. Biol. & Med., *103*:177 (January), 1960. 3. Griffith, R. S.: Comparison of Antibiotic Activity in Sera after the Administration of Three Different Penicillins, Antibiotic Med. & Clin. Therapy, 7:129 (February), 1960. 4. Editorial: New England J. Med., *263*:361 (August 18), 1960. 5. Editorial: New York J. Med., *60*:498 (February 15), 1960.

Superficial venography (radiograph on Kodak Blue Brand Medical X-ray Film) demonstrates tortuous collateral circulation in abdominal wall.

Splenoportograms demonstrate abdominal hepatic circulation, gastric varices (GV), umbilical vein (UV), coronary vein (CV), splenic vein (SV), caput medusae (CM).

PORTACAVAL SHUNT

in Cruveilhier-Baumgarten Syndrome

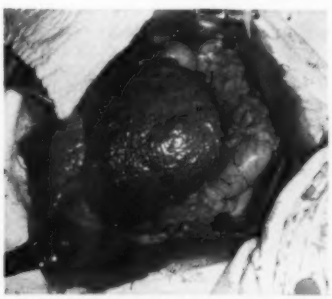
Procedure highlighted by reproductions of radiographs and full-color transparencies

Study the procedure outlined herewith. Notice how words and pictures work together, making each step clear, memorable. Truly, records such as these are *brilliant* aids to medicine.

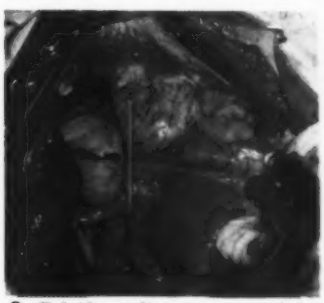
The Cruveilhier-Baumgarten Disease* results from a congenital hypoplastic liver with obliteration of portal venous radicals. Because of this, the umbilical vein fails to close at birth. Ultimately, this collateral channel becomes tortuous and highly resistant, and frank portal hypertension with all its sequelae develops. An enlarged spleen, a small hypoplastic and often cirrhotic liver with good function, and a caput medusae with a venous hum are the characteristics of this disease.

*The Cruveilhier-Baumgarten Syndrome is reserved for those instances of cirrhosis in which a caput medusae and venous hum occur secondarily to canalization of the umbilical vein.

1. Thoracolumbar incision: Ninth rib is resected through its periosteal bed thus preserving the congenitally patent umbilical vein.



2. Abdomen and chest opened, diaphragm divided. Liver—entire right lobe visible—cirrhotic, characteristically small. Fundus of gallbladder and hepatic flexure of colon are seen.



3. Falciform ligament containing umbilical vein. Note probe in foramen of Winslow; also dilated veins of Retzius below retractor, common duct, gallbladder, duodenum and pylorus.

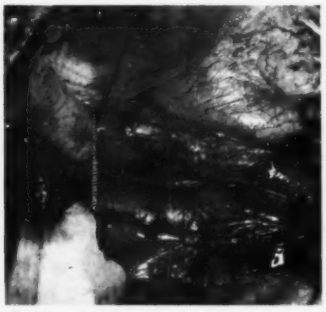
PORTACAVAL SHUNT *(continued)*

4. Triple lumen catheter threaded into portal vein via jejunal vein to determine extended portal pressures. (Recorded at 36 cm. of saline.)

5. Inferior vena cava partially exposed. Duodenum (A), head of pancreas (B), partially mobilized. Anomalous right hepatic artery (C) hides portal vein.

6. Common duct (A), duodenum (B), gallbladder (C), anomalous hepatic artery between common duct and inferior vena cava are visible.

7. Pancreas, under surface, clearly visible. Only anterior surface of the vena cava is exposed.



8. Portal vein seen beneath common duct (blue green). Hepatic artery dissected free and reflected downward.

9. Portal vein now dissected. Note its enormous size. Hepatic artery displaced medially.

10. Satinsky clamp partially occludes inferior vena cava; small retractor opens portal vein. Posterior row of side-to-side anastomoses shown.

11. Anterior row of anastomoses completed. Bulldog clamp occludes portal vein in hepatic side; large Blakemore clamp occludes portal vein.

12. Clamps removed. Anastomoses filled out, blood is coursing through. Final portal pressure was recorded at 10 cm. of saline.

From Kodak come medical x-ray films—Kodak Blue Brand and Kodak Royal Blue, Kodak's fastest x-ray film, designed to assure minimum exposure for each examination. **Kodak color materials** are available for every photographic purpose. *For miniature and motion-picture cameras*, there is Kodachrome Film; *for sheet-film cameras*—Kodak Ektachrome Film and Kodak Ektacolor Film; *for roll-film and miniature cameras*—Kodak Ektachrome Film and Kodacolor Film. Also a variety of Kodak color print materials is available.

Order Kodak x-ray products from your Kodak x-ray dealer, Kodak photographic products from your Kodak photographic dealer.

Kodak
TRADE MARK

Medical Division, EASTMAN KODAK COMPANY, Rochester 4, N.Y.

Culture plate with heavy growth of Staphylococcus aureus. Zone of complete inhibition produced by placing on plate a paper letter "Z" which had been dipped into Zephiran Chloride aqueous solution 1:1000.

Zephiran® CHLORIDE

(BRAND OF REFINED BENZALKONIUM CHLORIDE)

kills resistant STAPHylococci in seconds

Winthrop LABORATORIES / New York 18, N. Y.

1438M

ULTRASHORT-ACTING... In diagnostic and surgical procedures SURITAL provides— ☐ rapid, smooth induction ☐ evenly sustained surgical plane of anesthesia ☐ prompt, pleasant recovery ☐ relative freedom from laryngospasm and bronchospasm. Detailed information on SURITAL sodium (thiamylal sodium, Parke-Davis) is available on request.

PARKE, DAVIS & COMPANY DETROIT 32, MICHIGAN

NOW AVAILABLE

A Surgical Library

SURGERY
Gynecology & Obstetrics

With International Abstracts of Surgery

Volumes I to III
July 1905 to *December* 1960, inclusive
in handsome buckram binding,
gold stamped
Specially priced at $2250.00
domestic shipping charges included

THIS IDEAL LIBRARY for the surgeon may be had in a color of buckram of your own choosing and without additional charge your name in gold lettering may be included on the binding. As it has taken us some time to accumulate these issues we suggest your early inquiry.

SURGERY, *Gynecology & Obstetrics*
54 EAST ERIE STREET • CHICAGO 11, ILLINOIS

NEW TECHNIQUES NEED *Castle* "80 SERIES" TWINLIGHTS

Snap-on sterilizable handles allow surgeon or assistant to control lighting themselves.

Specialized lighting is needed today for simultaneous illumination of separate surgical sites, or to penetrate the blind recesses of massive wounds.

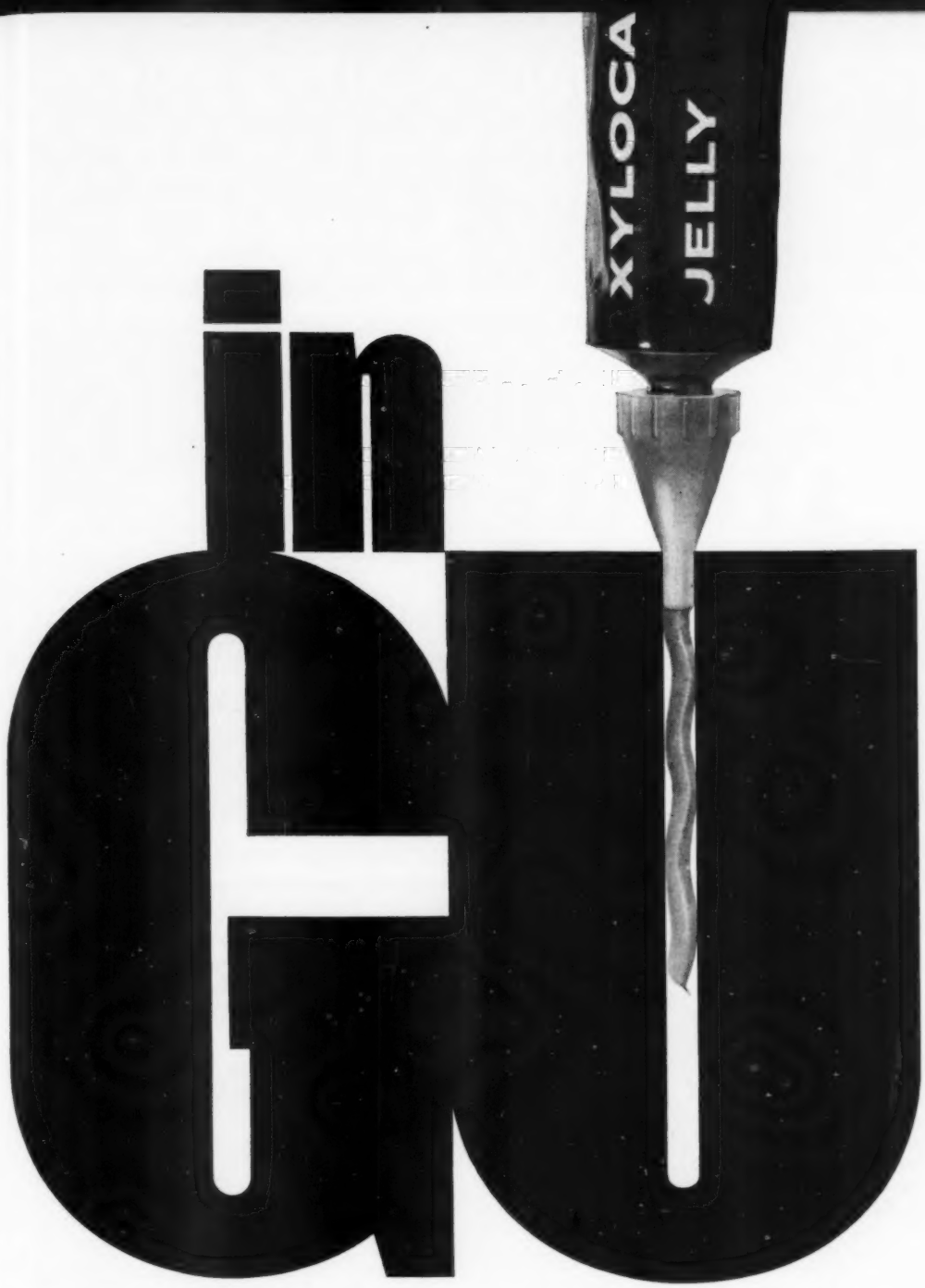
Castle "80 Series" Twinlights meet this need with twin 25-inch diameter lampheads mounted on 9-foot tracks, allowing light to be beamed to the field from almost any angle. Dual angulated beams insure over-all wound coverage, without need for constant lamphead positioning. Illumination is color-corrected, with shadow and glare reduced to a minimum.

And, the Kryo-Lux Heat Filter—developed as a result of studies of the effect of increased temperature on cerebro-spinal fluids—makes the "80 Series" one of the coolest surgical lights ever built.

Ask your Castle dealer for full information, or write us.

Castle LIGHTS AND STERILIZERS

WILMOT CASTLE CO., 1809-12 E. HENRIETTA RD., ROCHESTER 18, N.Y.



Xylocaine®Jelly, BRAND OF LIDOCAINE* topical anesthetic, brings fast and long lasting relief and relaxation during painful cystoscopy, sounding, and catheterization. Its water-soluble base adheres to the urinary mucosa; it is nonstaining, nonirritating, nonsensitizing. Xylocaine Jelly lubricates as well as anesthetizes to facilitate instrumentation.

Composition: Xylocaine Jelly contains 2% Xylocaine hydrochloride in a sterile, aqueous vehicle of suitable viscosity. Dose: 5 cc. to 30 cc. is applied topically, depending on the procedure. Available in 30 cc. collapsible tubes. Astra Pharmaceutical Products, Inc., Worcester 6, Massachusetts, U.S.A. *U.S. Pat. No. 2,441,498. Made in U.S.A.

STERILE CAMERA

Designed by surgeons especially for use by surgeons

- completely automatic and aseptic
- color or black and white photos
- already many enthusiastic users

"excellent detail and focus depth" write:

WATERS CORP.

Dept. 4
P.O. Box 288
Rochester, Minn.

regional representatives at your service.

A logical prescription for overweight patients

anorectic-ataractic

BAMADEX®

meprobamate 400 mg., with d-amphetamine sulfate 5 mg., Tablets

meprobamate **plus** d-amphetamine... depresses appetite...elevates mood... eases tensions of dieting...**without** overstimulation, insomnia or barbiturate hangover.

Dosage: One tablet one-half to one hour before each meal.

Lederle

THE IMPROVED PADGETT-HOOD

Manual

DERMATOME

WITH ALUMINUM DRUM

•

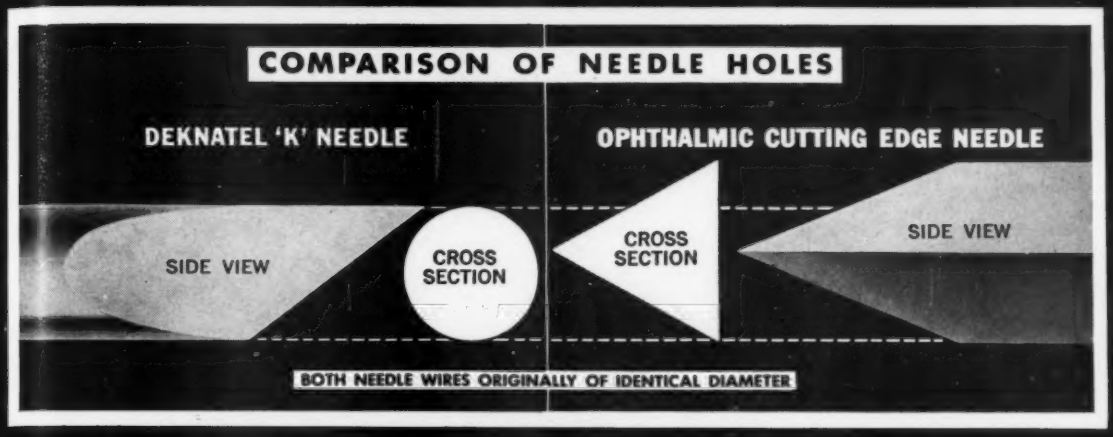
SIMPLIFIES SKIN GRAFTING

Accurate and uniform grafts up to 4 inches wide, 8 inches in length. Inexpensive **THROW-AWAY BLADES, DERMATONE TAPE,** and other accessories available for all models. Guaranteed.

For Complete Information Write

KANSAS CITY ASSEMBLAGE CO.
111 EAST GREGORY BLVD.
KANSAS CITY 14, MISSOURI

FOR PLASTIC CLOSURE OF SKIN
USE THE FINER GAUGES OF THE
DEKNATEL 'K' NEEDLE



Penetrating point is completely within cross-sectional diameter of wire. Because the point is ground, there is no enlargement of the wire. There are no cutting sides.

Formation of the triangular point inevitably enlarges the wire beyond its original diameter. The three cutting sides project beyond the original cross-section.

A FEW OF THE MANY ADVANTAGES AFFORDED BY THE DEKNATEL 'K' NEEDLE

SKIN CLOSURES WITH FINER GAUGE NEEDLES THAN EVER USED BEFORE. Closure is readily made with a 6-0 arteriovascular-type needle (as illustrated below) – a finer diameter than the equivalent opthalmic needle. This finer diameter produces superior cosmetic results and decreases the scarring potential.

SHARPER THAN CONVENTIONAL CUTTING NEEDLES YET LEAVES A TAPER POINT HOLE. Unlike conventional needles whose cutting blades project beyond the diameter of the wire, the Deknatel 'K' Needle point is completely within the normal diameter. The hole is therefore that of a taper point needle – the smallest the wire can make. There are no lateral projections in any plane to enlarge the hole.

EXTREMELY FINE PICKUP WITHOUT TEARING OR CUTTING OUT OF TISSUE. The absence of cutting sides and the orientation of the point allow the pickup of finest sections with minimal trauma. There is no cutting in, out or laterally. Subcuticular layers may be picked up with almost microtome thinness if desired. The very edges of skin are coapted with ease.

NOW AVAILABLE

KT-1 KT-2 KH-3

CODE NO.	NEEDLE	SUTURE	SIZE
9834	KT-1	SILK	6-0
9835	KT-1		5-0
9836	KT-2		6-0
9837	KT-2		5-0
9838	KH-3		6-0
9839	KH-3		5-0
9840	KT-1	NYLON	6-0
9841	KT-1		5-0
9842	KT-2		6-0
9843	KT-2		5-0
9844	KH-3		6-0
9845	KH-3		5-0
9846	KT-1	DERMAL	5-0
9847	KT-2		5-0
9848	KH-3		5-0

All sutures are 18" length

MAIL THIS COUPON FOR SAMPLES AND COMPLETE DATA

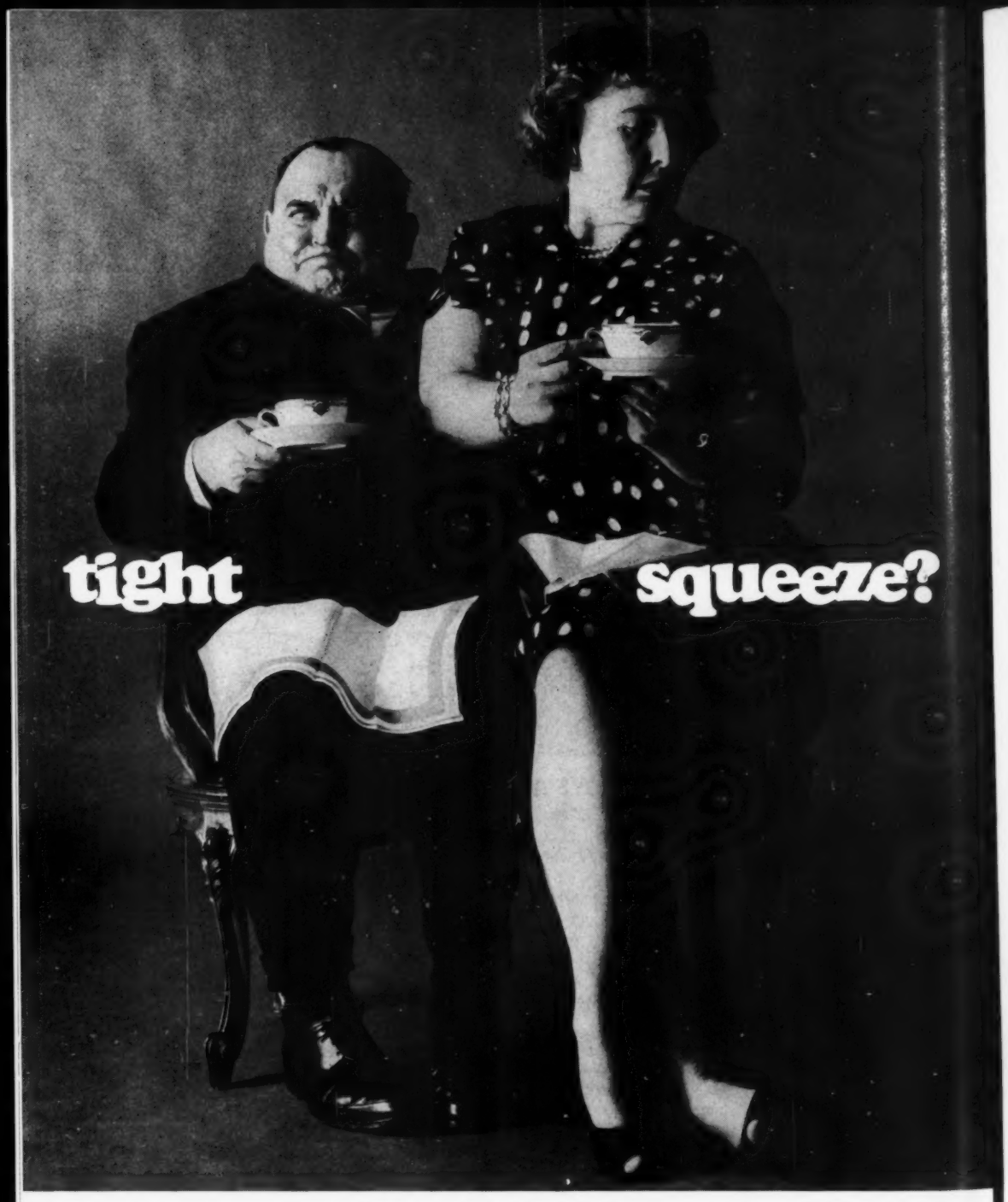
DEKNATEL, 96-62 222 Street, Queens Village 29, N.Y.
Please send samples of Deknatel 'K' Needle:

CODE NO._____

DR._____

STREET_____

CITY_____ ZONE_____ STATE_____



NEEDED: THE APPETITE SUPPRESSANT STRONG ENOUGH AND SAFE ENOUGH TO DO THE JOB

Ambar controls many cases of overeating/obesity refractory to usual therapy. To strengthen the will for successful dieting, the methamphetamine-phenobarbital in Ambar is designed to improve mood without harmful CNS overstimulation. Available in different forms to enable individualization of dosage: **AMBAR #1 EXTENTABS,** 10-12 hour extended action tablets, methamphetamine HCl 10.0 mg., phenobarbital 64.8 mg. **AMBAR #2 EXTENTABS,** methamphetamine HCl 15.0 mg., phenobarbital 64.8 mg. Also conventional **AMBAR TABLETS,** methamphetamine 3.33 mg., phenobarbital 21.6 mg.

Robins

A. H. ROBINS CO., INC., RICHMOND 20, VA.

Ambar™ #1 Extentabs® / Ambar™ #2 Extentabs®

a new, improved, more potent relaxant for anxiety and tension

- effective in half the dosage required with meprobamate
- much less drowsiness than with meprobamate, phenothiazines, or the psychosedatives
- does not impair intellect, skilled performance, or normal behavior
- neither depression nor significant toxicity has been reported

alert tranquillity

Striatran®

EMYLCAMATE

- a familiar spectrum of antianxiety and muscle-relaxant activity
- no new or unusual effects—such as ataxia or excessive weight gain
- may be used in full therapeutic dosage even in geriatric or debilitated patients
- no cumulative effect
- simple, uncomplicated dosage, providing a wide margin of safety for office use

STRIATRAN is indicated in anxiety and tension, occurring alone or in association with a variety of clinical conditions.

Adult Dosage: One tablet three times daily, preferably just before meals. In insomnia due to emotional tension, an additional tablet at bedtime usually affords sufficient relaxation to permit natural sleep.

Supply: 200 mg. tablets, coated pink, bottles of 100.

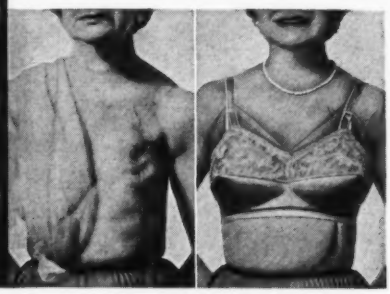
While no absolute contraindications have been found for Striatran in full recommended dosage, the usual precautions and observations for new drugs are advised.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

STRIATRAN IS A TRADEMARK OF MERCK & CO., INC.

after mastectomy



A mastectomy patient wearing IDENTICAL FORM

your patient's most important back-to-normal step

IDENTICAL® FORM

The importance of treating the whole patient is nowhere more graphically illustrated than in the successful rehabilitation of the mastectomy patient. With the post-operative fitting of IDENTICAL FORM — the life-like breast prosthesis — women look natural and feel better immediately. Made of soft skin-like plastic, IDENTICAL FORM contains a flowing gel that simulates the natural movement and weight of the normal breast. With IDENTICAL FORM your patient won't experience the discomfiture of static, dragging weight or "riding-up". Normal contour, comfort and confidence are maintained even when she wears an evening gown or bathing suit.

You'll find our new booklet "*Total Care of Your Mastectomy Patient*" invaluable as a guide for all the physiological needs of your mastectomy patient.

Available in 24 sizes. Expertly fitted by authorized dealers and adaptable to any brassiere. Patented U.S.A. & foreign countries.

IDENTICAL FORM, INC.
17 West 60th St., New York 23, N. Y.
Please send professional literature and list of authorized dealers.

.....M.D.

Address.....

City.....State.....

IN BRIEF

Vistaril®
HYDROXYZINE HYDROCHLORIDE
Parenteral Solution

Vistaril is a rapid-acting calmative with a wide margin of safety. Its use preoperatively generally permits a reduction in dosage of narcotics and barbiturates. Vistaril's antiemetic properties further enhance its usefulness pre- and postoperatively.

ACTIONS & INDICATIONS: Vistaril, as part of a preoperative regimen, can safely relax your patients by allaying fear and apprehension.

ADVANTAGES: Vistaril produces a calming effect without hypnosis. Vistaril provides direct and secondary muscle relaxation. Vistaril apparently is nonaddicting — discontinuance after months of treatment has not produced withdrawal symptoms. Vistaril has a remarkable record of safety, when used in recommended dosage. Unlike the phenothiazines, parkinsonism and blood or liver toxicities have not been reported with Vistaril. Unlike the rauwolfia derivatives, Vistaril acts rapidly, does not increase gastric secretions, and there have been no reports of nasal congestion, drug-induced depression, or sinusitis associated with its use. Unlike the meprobamates, there have been no reports of incoordination, ataxia, abdominal discomfort, anorexia, nausea, vomiting, diarrhea, allergic dermatitis, or anaphylactic reactions. VISTARIL PARENTERAL SOLUTION permits rapid action and may be given via I.M. or I.V. routes.

CONTRAINDICATIONS: There are no known contraindications to Vistaril.

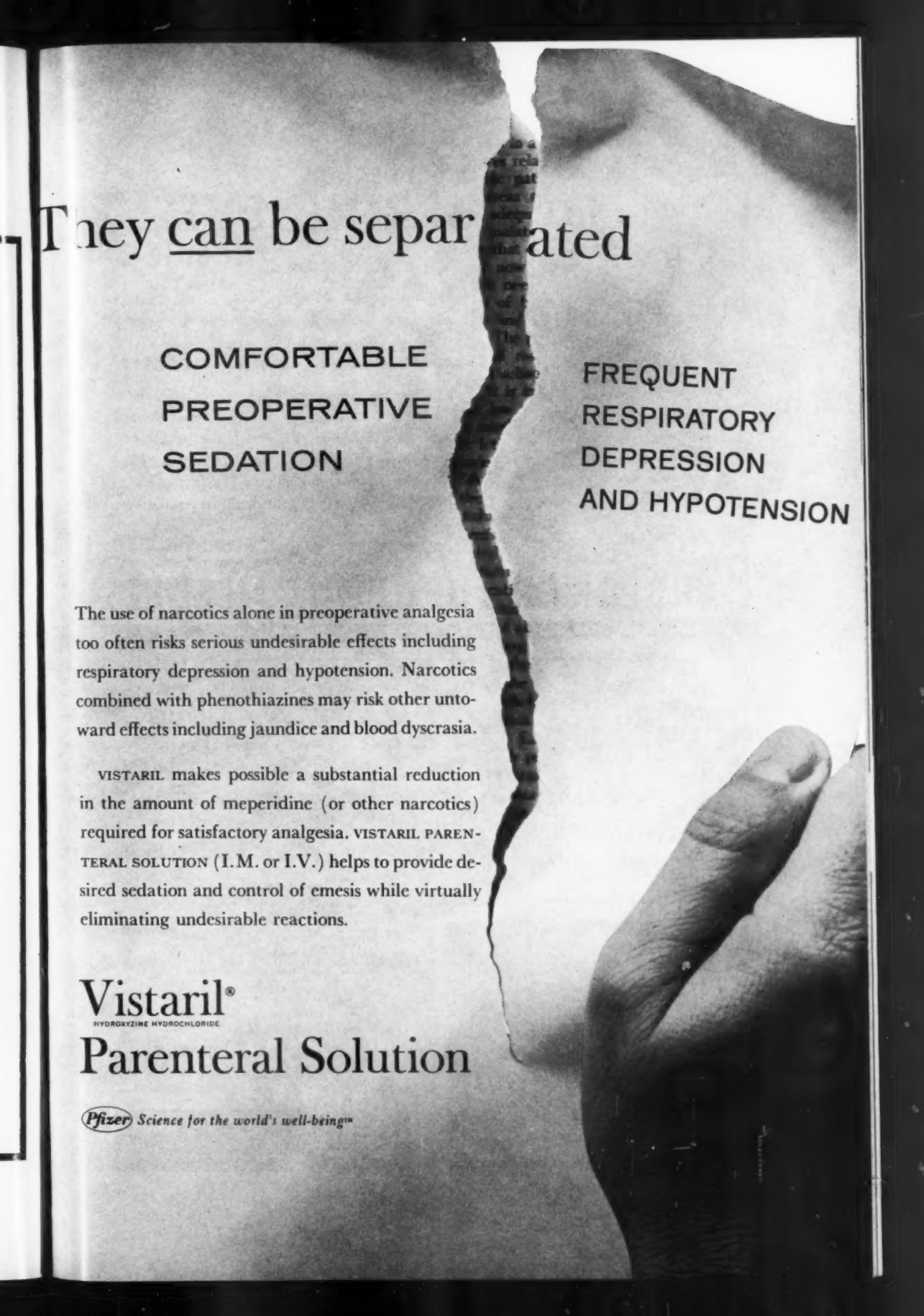
SIDE EFFECTS AND PRECAUTIONS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing upon reduction of dosage or within a few days of continued therapy. Dryness of mouth may be encountered at higher dosages. The potentiating action of hydroxyzine must be taken into consideration when it is used in conjunction with C.N.S. depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is for 24-48 hours, unless changed by judgment of physician

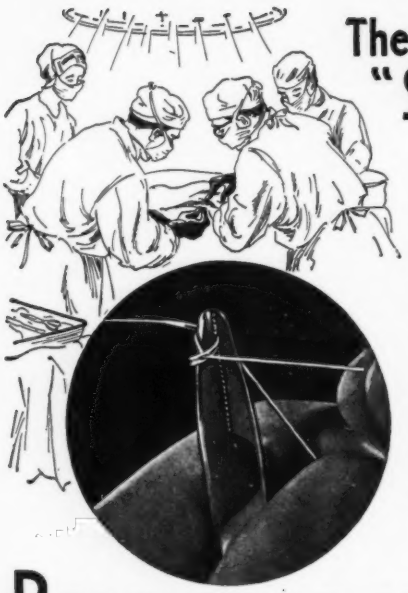
ADMINISTRATION AND DOSAGE: Vistaril dosage varies with the state and response of each patient, rather than on a weight basis. Dosage should be individualized by the physician for optimum results. The usual parenteral dosage in preoperative sedation for adults is 25-50 mg. I.M. or I.V. q. 4 h., p.r.n., (alone or in conjunction with reduced dosages of narcotics); for children, 0.5 mg./lb. body weight I.M.

HOW SUPPLIED: *Vistaril Parenteral Solution*—10 cc. vials and 2 cc. Steraject® Cartridges, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc. *Vistaril Capsules* (as the pamoate)—25, 50, and 100 mg. *Oral Suspension* (as the pamoate)—25 mg. per 5 cc. teaspoonful.

More detailed professional information available on request.

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.


They can be separated
COMFORTABLE PREOPERATIVE SEDATION
FREQUENT RESPIRATORY DEPRESSION AND HYPOTENSION
The use of narcotics alone in preoperative analgesia too often risks serious undesirable effects including respiratory depression and hypotension. Narcotics combined with phenothiazines may risk other untoward effects including jaundice and blood dyscrasia.
VISTARIL makes possible a substantial reduction in the amount of meperidine (or other narcotics) required for satisfactory analgesia. VISTARIL PARENTERAL SOLUTION (I.M. or I.V.) helps to provide desired sedation and control of emesis while virtually eliminating undesirable reactions.
Vistaril®
HYDROXYZINE HYDROCHLORIDE
Parenteral Solution
Pfizer Science for the world's well-being™



The Berbecker "SPRING-EYE" Needle

THE BERBECKER Spring Eye may be threaded at any point on the suture merely by forcing the suture through the slot into place. It is then held as securely as though in a solid eye.

This eye permits use of black silk or other non-absorbable sutures, as used in the Halsted technique, for stomach and other abdominal operations, where tension on the wound is excessive. One of many dependable Berbecker needles obtainable regularly at your surgical supply dealer.

JULIUS BERBECKER & SONS. INC.
15A EAST 26th STREET • NEW YORK 10, N. Y.

BERBECKER SURGEONS' NEEDLES

Made in England for the Surgeons and Hospitals of America

BAMADEX

meprobamate 400 mg., with d-amphetamine sulfate 5 mg., tablets

anorectic-ataractic

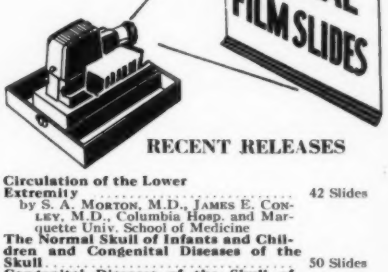
A logical combination for appetite suppression

meprobamate **plus** d-amphetamine...suppresses appetite...elevates mood... reduces tension...**without** insomnia, overstimulation or barbiturate hangover.

Dosage: One tablet one-half to one hour before each meal.

Lederle

Fits any 2" x 2" Viewer or Projector



RECENT RELEASES

2-4	**Circulation of the Lower Extremity** by S. A. MORTON, M.D., JAMES E. CONLEY, M.D., Columbia Hosp. and Marquette Univ. School of Medicine	42 Slides
3-1A	**The Normal Skull of Infants and Children and Congenital Diseases of the Skull**	50 Slides
3-1B	**Congenital Diseases of the Skull of Infants and Children (Cont'd. from Set 3-1A) and Traumatic Disorders of the Skull**	50 Slides
4-1	**Atlas of Spinal Cord Lesions (excluding discs)** by J. E. WHITELEATHER, M.D., Dir. Dept. Radiology, Baptist Mem Hosp., Memphis, Tenn.	50 Slides
7-3A	**Benign Surgical Lesions of the Genito-urinary Tract**	51 Slides
7-3B	**Malignant Surgical Lesions of the Genitourinary Tract** by IRA H. LOCKWOOD, M.D., Research Clinic, Kansas City Mo., and Associates	54 Slides

PRICE PER SERIES $16.50

ORDER DIRECT or WRITE for complete descriptions.

MXRR
MEDICAL FILM SLIDE DIVISION
MICRO X-RAY RECORDER, INC.
3755 W. Lawrence • Chicago 25, Illinois

For positive intestinal intubation the CANTOR® TUBE provides:

Ease of intubation—Successful passage in 96% of cases. Free flowing mercury in soft pliable bag tip facilitates movement down alimentary canal.

Efficient decompression—Larger internal diameter. Less possibility of plugging.

Freedom from irritation—No metal parts which might injure mucosa.

Assured safety—Special composition bag tip. Has low permeability to gases. Will not distend, particularly during long periods of intubation.

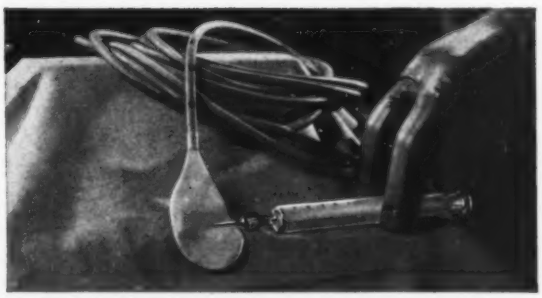
Try the **Genuine Cantor Tube** at your first opportunity. Proven through years of extensive use.

Available in Adult Size, 16 Fr., 10' long
Child Size, 12 Fr., 7' long

Either size complete with bag...$7.50
Replacement bags, Child or Adult sizes...$.70

Order From Your Surgical Supply Dealer

Clay-Adams
NEW YORK 10



Syringe technic for simultaneously introducing mercury, aspirating air, and creating safety valve (needle hole releases gases without allowing mercury to escape).

resistant
staphylococci
among
outpatients
emerge
less
frequently...
disappear
more
readily

CHLOROMYCETIN

chloramphenicol, Parke-Davis

"Resistance to chloramphenicol was surprisingly infrequent (0-5%)" among strains of staphylococci isolated from outpatients over a 5-year period. It was impressive to note that less than 6% of 310 strains isolated from patients treated in the emergency room were resistant to CHLOROMYCETIN. Moreover, it would appear "...that chloramphenicol-resistant staphylococci disappear more readily after leaving the hospital environment."[1]

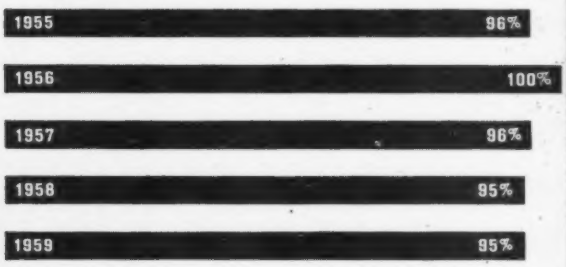
Goslings and Büchli[2] report that "...resistance was lost entirely after 3 months..." in the small percentage of patients who carried staphylococcal strains resistant to CHLOROMYCETIN. Numerous other investigators concur in the observation that staphylococcal resistance to CHLOROMYCETIN is of a low order.[3-8]

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

References: (1) Bauer, A. W.; Perry, D. M., & Kirby, W. M. M.: *J.A.M.A.* 173:475, 1960. (2) Goslings, W. R. O., & Büchli, K.: *Arch. Int. Med.* 102:691, 1958. (3) Goodier, T. E. W., & Parry, W. R.: *Lancet* 1:356, 1959. (4) Fisher, M. W.: *Arch. Int. Med.* 105:413, 1960. (5) Petersdorf, R. G., *et al.*: *Arch. Int. Med.* 105:398, 1960. (6) Glas, W. W., in Symposium on Antibacterial Therapy, Michigan & Wayne County Acad. Gen. Pract., Detroit, September 12, 1959, p. 7. (7) Modarress, Y.; Ryan, R. J., & Francis, Sr. C. E: *J. M. Soc. New Jersey* 57:168, 1960. (8) Rebhan, A. W., & Edwards, H. E.: *Canad. M. A. J.* 82:513, 1960.

IN VITRO SENSITIVITY OF COAGULASE-POSITIVE STAPHYLOCOCCI TO CHLOROMYCETIN FROM 1955 TO 1959*



These sensitivity tests were done by the disc method on 310 strains of coagulase-positive staphylococci. Strains were isolated from patients seen in the emergency room. It should be noted that among inpatients, resistant strains were considerably more prevalent.

*Adapted from Bauer, Perry, & Kirby[1]

10260

PARKE-DAVIS

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

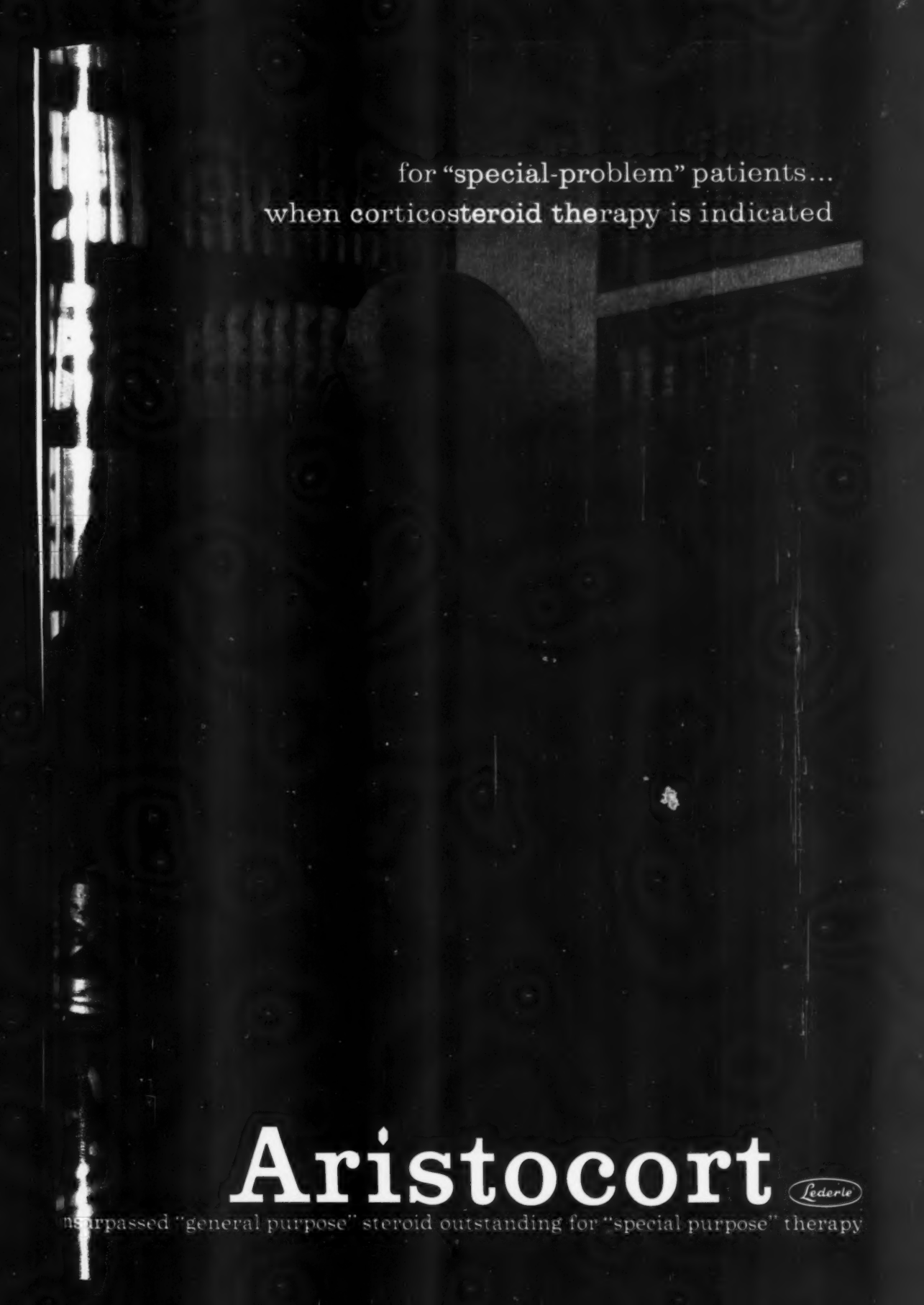
A biochemical compound used to diminish intestinal gas in healthy persons and those patients having digestive disorders ■

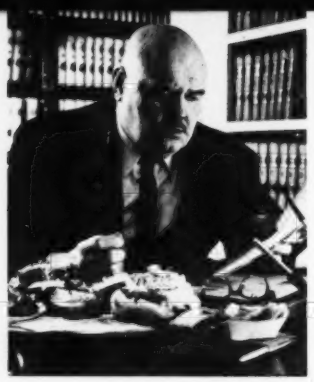
KANULASE

Each Kanulase tablet contains Dorase,* 320 units, combined with pepsin, N.F., 150 mg.; glutamic acid HCl, 200 mg.; pancreatin, N.F., 500mg.; oxbile extract, 100 mg. Dosage: 1 or 2 tablets at mealtime. Supplied: Bottles of 50 tablets.

*DORASE BRAND OF CELLULASE, EXPRESSED AS DIGESTIVE ACTIVITY UNITS.

SMITH-DORSEY • a division of The Wander Company • Lincoln, Nebraska


for "special-problem" patients...
when corticosteroid therapy is indicated
Aristocort
Lederle
nsurpassed "general purpose" steroid outstanding for "special purpose" therapy



in rheumatoid arthritis

Aristocort®

Triamcinolone LEDERLE

UNSURPASSED "GENERAL-PURPOSE" STEROID OUTSTANDING FOR "SPECIAL-PURPOSE" THERAPY

ARISTOCORT Triamcinolone has long since proved its *unsurpassed efficacy and relative safety* in treating rheumatoid arthritis. Mounting clinical evidence has shown that ARISTOCORT is also highly valuable for the "special-problem" arthritic – the patient who, because of certain complications, was hitherto considered a poor candidate for corticosteroids.

for example:

SPECIAL PROBLEM: ANXIETY-TENSION

When triamcinolone was used, euphoria and psychic unrest rarely occurred. (McGavack, T. H.: *Clin. Med.* 6:997 [June] 1959.)

SPECIAL PROBLEM: OVERWEIGHT

No patient developed voracious appetite on triamcinolone. Preferable for the overweight person whose appetite is undesirably stimulated by other steroids. (Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L.: *Arthritis & Rheumatism* 1:215 [June] 1958.)

SPECIAL PROBLEM: EDEMA

Since it does not produce edema, triamcinolone is useful in rheumatoid arthritis patients with cardiac decompensation who need steroid therapy. (Hollander, J. L.: *J.A.M.A.* 172:306 [Jan. 23] 1960.)

SPECIAL PROBLEM: HYPERTENSION

Triamcinolone may be included among the currently available antirheumatic steroids having the least tendency to cause sodium retention. (Ward, L. E.: *J.A.M.A.* 170:1318 [July 11] 1959.)

Hypertension did not result from triamcinolone therapy. Existing hypertension was reduced sometimes. This may have been due to lack of sodium retention. (Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L.: *Arthritis & Rheumatism* 1:215 [June] 1958.)

Precautions: Collateral hormonal effects generally associated with corticosteroids may be induced. These include Cushingoid manifestations and muscle weakness. However, sodium and potassium retention, edema, weight gain, psychic aberration and hypertension are exceedingly rare. In the treatment of rheumatoid arthritis, dosage should be individualized and kept at the lowest level needed to control symptoms. Dosage should not exceed 36 mg. daily without potassium supplementation. Drug should not be withdrawn abruptly. Contraindicated in herpes simplex and chicken pox.

Supplied: Scored tablets—1 mg. (yellow); 2 mg. (pink); 4 mg. (white); 16 mg. (white). Also available—syrup, parenteral and various topical forms.

Lederle

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

"highly recommended for preoperative preparation of the colon"[1]

KANTREX®

CAPSULES

—for local effect in gastrointestinal tract; not for systemic infections

After studying 30 different drugs and combinations, Cohn and Longacre concluded that oral KANTREX is "one of the most effective agents yet developed for intestinal antisepsis."[2]

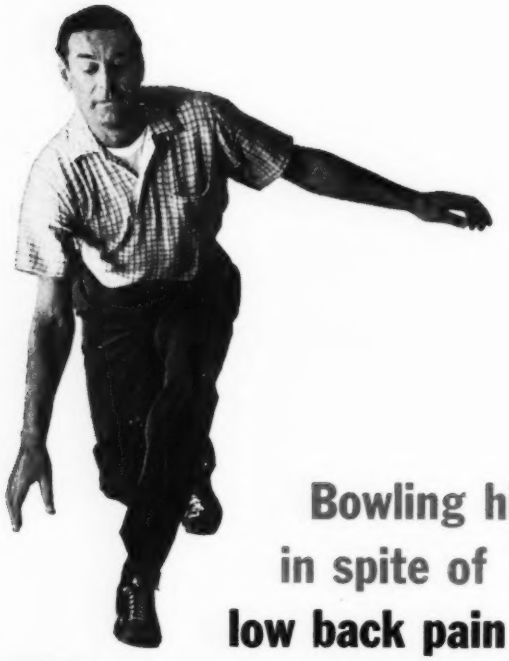
1. Cohn, L., Jr., and Longacre, A. B.: Antibiotics Annual 1958-9, p. 761.
2. Cohn, L., Jr., and Longacre, A. B.: S. G. & O. 108:100, 1959.

SUPPLY: KANTREX Capsules, 0.5 Gm. kanamycin (as sulfate), bottles of 20 and 100.

Comprehensive information in official package circular or available on request.

BRISTOL LABORATORIES, SYRACUSE, N. Y.

Bristol™



Bowling his best in spite of low back pain

Trancopal

BRAND OF CHLORMEZANONE

relaxes skeletal muscle spasm

The "tranquilaxant," Trancopal, quickly relieves skeletal muscle spasm and pain associated with low back syndrome, torticollis, sprains and strains, and arthritis. At the same time, its tranquilizing action reduces restlessness and irritability, making the patient more amenable to physical therapy. In a group of 193 patients with various musculoskeletal disorders, treatment with Trancopal brought good to excellent results to 162. "... the combined effect of tranquilization and muscle relaxation enabled them to resume their normal duties in from twenty-four to forty-eight hours."[1] "... the most promising muscle relaxant presently available. Its outstanding characteristics are safety, excellent tolerance and potency."[2]

Dosage: Adults, 200 mg. orally three or four times daily; in some instances 100 mg. three or four times daily suffice. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

How Supplied: Trancopal Caplets®
200 mg. (green colored, scored), bottles of 100.
100 mg. (peach colored, scored), bottles of 100.

1. Kearney, R. D.: *Current Therap. Res.* 2:127, April, 1960. 2. Cohen, A. I.: *Current Therap. Res.* 2:374, Aug., 1960.

Trancopal (brand of chlormezanone) and Caplets, trademarks reg. U. S. Pat. Off.

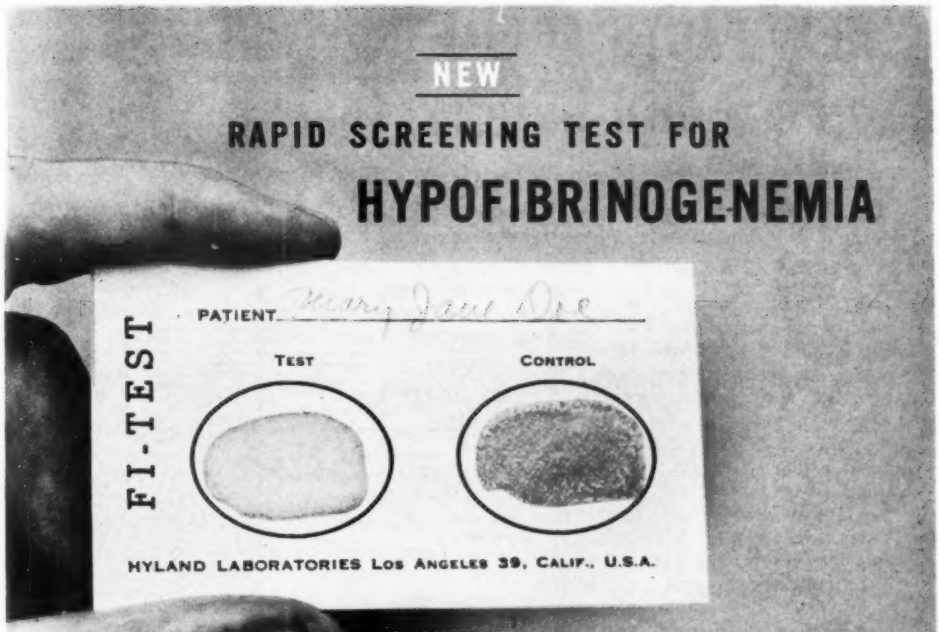
Winthrop LABORATORIES, New York 18, N. Y.

1530M

NEW

RAPID SCREENING TEST FOR

HYPOFIBRINOGENEMIA



FI-TEST*

Test results at patient's bedside – from skin puncture to reading – in less than 2 minutes. Only one drop of blood required. Test performed by simple, rapid-slide technic.

FI-TEST indicates whether fibrinogen content is above or below 100 mg-%, the concentration considered critical. Easy-to-read results indicate promptly whether or not replacement fibrinogen is needed. (If reading shows a normal fibrinogen level, needless replacement therapy may be avoided and the physician is alerted to seek another explanation for continued bleeding.)

Supplied in compact ready-to-use kits containing complete materials for 6 determinations.

*TRADEMARK OF HYLAND LABORATORIES

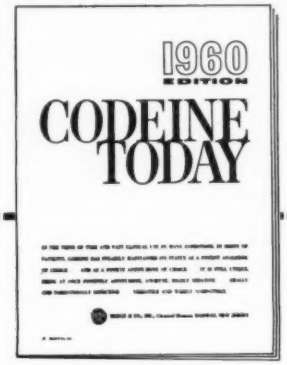
HYLAND

Hyland

HYLAND LABORATORIES
4501 Colorado Blvd., Los Angeles 39, Calif.
160 Lockwood Ave., Yonkers, N.Y.

NEW FACTS ABOUT CONTROLLING PAIN AND COUGH

New Comprehensive Supplement to 'Codeine Today' Highlights Newest Data on One of Medicine's Most Useful but Underestimated Drugs



Just 20 minutes reading will review for you essential clinical findings on the use of Codeine. New supplement presents concise quotes by today's authorities on the use of codeine in conditions from the common cold to sickle cell disease. Tells when to use, how to use and where to use this versatile drug. Supplement is attached to 'Codeine Today' which reviews 1957-1958 data. This information is of interest to practically every practitioner. Bibliography now totals more than 80 references.

MERCK

SEND FOR YOUR FREE COPY TODAY

MERCK & CO., INC., Medicinal Products Department
Rahway, New Jersey

Please send me_____copies of Codeine Today with new 7-page supplement.

PHYSICIAN'S NAME AND ADDRESS

THE UNIVERSITY OF TEXAS,

POSTGRADUATE SCHOOL OF MEDICINE

Affiliated Hospitals:

The University of Texas M. D. Anderson Hospital and Tumor Institute, St. Luke's Episcopal Hospital and St. Joseph's Hospital offer training in Anesthesiology to Graduates from Approved Medical Schools who have completed an approved internship of one year or more.

For information write

DR. WM. S. DERRICK,

6723 Bertner Avenue, Houston 25, Texas

Ann Woodward
Director

"In Time of"

Personnel

"Need" . . .

. . . the Woodward Bureau will

EXTEND your line of communication to many of the best qualified physicians in the country;

SAVE uncounted hours by utilizing our service for assembling data, screening applicants, checking references, and

SPEED UP the ultimate selection of the man you need.

The fact is, in recent months, we have accumulated a file of exceptionally fine candidates which can conceivably offer precisely the surgeon, gynecologist or obstetrician you are seeking as an associate for your office or clinic.

Whether you need a top ranking man to head a department, or a younger physician to associate himself with you or your group, the Woodward Bureau can *make your search easier and the results more rewarding.*

Our 63rd Year

WOODWARD
MEDICAL PERSONNEL BUREAU
FORMERLY AZNOES · 185 N. WABASH · CHICAGO

Founders of the counseling service to the medical profession, serving medicine with distinction over half a century.

Quigley and Banks—Progress in the Treatment of Fractures and Dislocations: 1950-1960

New!-the latest findings in handling fractures

This book gives you an unusually complete review of the advances and improvements in the management of fractures during the past 10 years. It represents a careful evaluation of all significant reports in the world literature since 1950. The authors add information from their own extensive experience on fracture service at the Peter Bent Brigham Hospital.

Here is just a few of the many problems and advances you will find discussed: evaluation of polyurethane foam in cases of non-union—role of arthrocentesis in fractures of the elbow—problem of differentiation of "sprained wrist" and fracture of the carpal scaphoid—evaluation of benefits of laminectomy in spinal fractures and timing of intervention—importance of open reduction of fractures of the knee—use of Lottes rod—etc.

This book is a reprinting of a 4-part article which appeared in the *New England Journal of Medicine* in the fall of 1960.

By THOMAS P. QUIGLEY, M.D., Assistant Clinical Professor of Surgery, Harvard Medical School, Surgeon, Peter Bent Brigham Hospital; and HENRY BANKS, M.D., Clinical Associate Professor in Orthopedic Surgery, Harvard Medical School, Associate in Orthopedic Surgery, Peter Bent Brigham Hospital. 102 pages, 5½"x7¾". $2.50. *New!*

Meares—A System of Medical Hypnosis

New!-tells how to use hypnosis safely and effectively in your practice

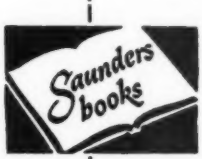
From the wide clinical experience of an eminent authority in the field, here is a sound, reasonable and practical explanation of the principles and use of hypnosis in medicine.

The author first sets forth solid information on every phase of modern hypnotic practice. He gives you step-by-step instructions for each method of induction—by direct stare, by suggestions for relaxation, by arm levitation. There is practical help on choosing the right method of induction for a particular case; on explaining to the patient just what you intend to do; and on handling his fears and unconscious defenses.

You'll find suggestions for clinical use of hypnosis in relief of pain and insomnia, as an aid to diagnosis, and as an anesthetic agent. The value of hypnosis in obstetrics and delivery is clearly discussed—with methods, problems and complications pointed up in rich detail. There is sound advice on applying hypnosis in the treatment of various gynecologic disorders, chronic illness, psychogenetic obesity, and alcoholism.

By AINSLIE MEARES, M.D., D.P.M., Melbourne, Australia. President, International Society for Clinical and Experimental Hypnosis. 484 pages, 6"x9¼". $10.00. *New—Just Ready!*

ORDER TODAY!



W. B. SAUNDERS COMPANY S.G.O.-12-60

West Washington Square, Philadelphia 5

☐ Quigley & Banks—Treatment of Fractures & Dislocations, 1950–60 . . . $ 2.50

☐ Meares—A System of Medical Hypnosis $10.00

Name----------

Address ----------

Watch for These Outstanding Features

In Future Issues of
SURGERY, *Gynecology and Obstetrics*
With International Abstracts of Surgery

ORIGINAL ARTICLES

CONTRIBUTIONS OF ENDOSTEUM, CORTEX, AND SOFT TISSUE TO OSTEOGENESIS. *C. Andrew L. Bassett, M.D., F.A.C.S., Daniel K. Creighton,* and *Frank E. Stinchfield, M.D., F.A.C.S.,* New York, New York.

CARTILAGE PHARYNGOPLASTY IN CLEFT PALATE PATIENTS. *Robert F. Hagerty, M.D.,* and *M. J. Hill, M.S.,* Charleston, South Carolina.

STUDIES ON THE REJECTION OF THE TRANSPLANTED HOMOLOGOUS DOG LIVER. *Thomas E. Starzl, M.D., Harry A. Kaupp, Jr., M.D., Donald R. Brock, M.D.,* and *James W. Linman, M.D.,* Chicago, Illinois.

THE PLICATION PROCEDURE IN THE TREATMENT OF SMALL BOWEL ADHESIONS. *Edgar J. Poth, M.D., F.A.C.S., Fred J. Wolma, M.D., F.A.C.S.,* and *John B. Lynch, M.D.,* Galveston, Texas.

RAPID IDENTIFICATION OF MALIGNANT CELLS IN VAGINAL SMEARS BY CYTOPLASMIC FLUORESCENCE. *Franklin R. Elevitch, M.D.,* and *Joel G. Brunson, M.D.,* Jackson, Mississippi.

AN ESTIMATION OF THE NITROGEN REQUIREMENTS FOR EQUILIBRIUM IN BURNED PATIENTS. *Harry S. Soroff, M.D., Major Elinor Pearson,* and *Curtis P. Artz, M.D., F.A.C.S.,* Fort Sam Houston, Texas.

RECONSTRUCTION OF THE COMMON BILE DUCT BY END-TO-END ANASTOMOSIS WITHOUT THE USE OF AN INTERNAL SPLINT OR STENT SUPPORT. *John L. Madden, M.D., F.A.C.S.,* and *William J. McCann, M.D., F.A.C.S.,* New York, New York.

COMPARATIVE LONG-TERM STUDY FOLLOWING PULMONARY RESECTION FOR TUBERCULOSIS. *G. H. Welch, Jr., M.D., W. H. Gentry, M.D., William F. Hollister, M.D., F.A.C.S.,* and *Will C. Sealy, M.D., F.A.C.S,* Durham, North Carolina.

SOME LABORATORY AND CLINICAL OBSERVATIONS ON COLY-MYCIN (COLISTIN) WITH PARTICULAR REFERENCE TO PSEUDOMONAS INFECTIONS. *Frank L. Meleney, M.D., F.A.C.S.,* and *George R. Prout, Jr., M.D.,* Miami, Florida.

COLLECTIVE REVIEWS

LOBECTOMY IN THE TREATMENT OF BRONCHOGENIC CARCINOMA. *T. W. Shields, M.D., F.A.C.S.,* Chicago, Illinois.

PSEUDOMEMBRANOUS (STAPHYLOCOCCAL) ENTEROCOLITIS. *John Van Prohaska, M.D., F.A.C.S., Farrell Mock, M.D., William Baker,* and *Ruth Collins,* Chicago, Illinois.

Abstracts of Current World Literature, Editorials, Book Reviews, The Surgeon at Work, The Book Shelf, and other special material will also appear throughout the year.

SURGERY, *Gynecology and Obstetrics*

54 East Erie Street, Chicago 11, Illinois

The Ideal Gift for Christmas

A COLLEAGUE

AN ASSOCIATE

A FRIEND

One Year $15.00

A Special Offer for

RESIDENTS · INTERNS · STUDENTS

One Year $10.00

I enclose my check for a one year subscription beginning with _____ issue. Send to:

Doctor_____

Address_____

City_____ Zone_____ State_____

☐ $15.00 Regular Subscription
☐ $10.00 Resident, Intern, Student Subscription
($2.00 Additional Postage outside United States and Canada)

Please enclose gift card. My name is:

Doctor_____

Address_____

City_____ Zone_____ State_____

SURGERY, *Gynecology and Obstetrics*

54 East Erie Street, Chicago 11, Illinois

THE SCIENTIFIC SOLUTION TO VASCULAR INSUFFICIENCY PROBLEMS

Jobst Pressure Gradient Fabric Supports are being used successfully in cases of Venous insufficiencies, Post-phlebitic syndrome, Post-operative inferior vena cava ligation, Ulcerations of the lower leg, Stasis dermatitis, Lymphedema and Post-fracture and injury edema.

Only Jobst Supports have controlled pressure gradients built into the supports to provide counter-pressure against internal hydrostatic pressure and assist in venous return.

Each Jobst Support is custom made to the individual patient's measurements.

For further information and prescription blanks, write to

JOBST INSTITUTE

THE JOBST INSTITUTE, INC.

1803 Jefferson Avenue • Toledo 2, Ohio

A LOGICAL ADJUNCT TO THE WEIGHT-REDUCING REGIMEN

meprobamate **plus** d-amphetamine... reduces appetite...elevates mood...eases tensions of dieting...**without** overstimulation, insomnia or barbiturate hangover.

Dosage: One tablet one-half to one hour before each meal.

anorectic-ataractic

BAMADEX®

meprobamate 400 mg., with d-amphetamine sulfate 5 mg., Tablets

Lederle

You need only ONE assistant when you use

SMITH

SELECTIVE RETRACTOR

(Patent Pending)

Big CLINIC Help for SMALL Hospitals

The Smith Retractor does ALL the retracting

Complete Description on Request

Exclusive Distributors

Codman & Shurtleff, Inc.

MAKERS OF SURGEONS' INSTRUMENTS

124 BROOKLINE AVENUE BOSTON 15, MASSACHUSETTS

ELECTRODYNE D-72 *External-Internal Defibrillator*

A proven instrument for clinical treatment of ventricular fibrillation through the closed chest.*

With closed chest cardiac massage NOW a reality – external defibrillation is a requisite for complete closed chest cardiac resuscitation

The countershock or impulse duration is automatically fixed and is optimum for effective ventricular defibrillation. Countershock voltage is variable in steps up to 750 volts, delivering up to 15 amperes through the chest wall. The D-72 was conservatively designed with these ratings in mind. Power relay contacts and isolation transformer safely transmit 12,000 watts. Automatic timing circuit will not allow successive countershocks more often than one per second, thus protecting the patient from undue heating. Maximum safety for patient and operator is provided by such features as the isolation transformer and thickly insulated handles of rubber backed 8.5 cm. diameter flat disc electrodes. This instrument is also available in combination with the well-known Electrodyne Cardiac Pacemaker.

Technical Data

***References:**

Nast, Philip R.; Pennypacker, Charles S.; Wagner, Joseph A.: Successful External Electrical Defibrillation in Acute Myocardial Infraction. Circulation, 22: 138-143, July, 1960.

Zoll, P. M., et al: Ventricular Fibrillation: Treatment and Prevention by External Electric Currents. The New England Journal of Medicine 262: 105, January 21, 1960.

Sasahara, Arthur A., Rudolph, Abraham M., Hoffman, Julien I. E., and Hauck, Anna J.: Ventricular Fibrillation during Catheterization of the Right Side of the Heart Terminated Successively by External Defibrillation. The New England Journal of Medicine, 261: 26, July 2, 1959.

Zoll, P. M., et al: Termination of Ventricular Fibrillation in Man by Externally Applied Electric Countershock. New England Journal of Medicine, 254: 727, April 19, 1956.

Information on the Electrodyne Cardioscope and other instruments is available on request.

Specialists in Medical Electronics

ELECTRODYNE

150 Endicott Street, Norwood, Massachusetts

EVERYONE IS RELIEVED WHEN URECHOLINE® Chloride (Bethanechol Chloride) REPLACES CATHETERIZATION

· *relief for the patient*

– prophylactic use of 'Urecholine' soon after surgery or childbirth often prevents painful urinary retention; therapeutically, 'Urecholine' rapidly facilitates micturition, without subjecting the patient to the discomfort of catheterization.

AFTER SURGERY AND CHILDBIRTH

URECHOLINE

HELPS CONTROL URINARY RETENTION – PHYSIOLOGICALLY

· *relief for the physician*

–'Urecholine' eliminates the danger of infection which often follows instrumentation.

· *relief for the nurse*

– prophylactic and therapeutic use of 'Urecholine' makes available valuable nursing time for other purposes.

supplied: 5 mg. and 10 mg. tablets, bottles of 100. 1-cc. ampuls containing 5 mg.

for additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

URECHOLINE IS A TRADEMARK OF MERCK & CO., INC.

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

saturation doses – the hard way!

Each of these food portions contains a saturation dose of one of the water-soluble B vitamins or C. The easy way to provide such quantities of these vitamins with speed, safety and economy is to prescribe Allbee with C. Recommended in pregnancy, deficiency states, digestive dysfunction and convalescence.

In each Allbee with C:		As much as:*
Thiamine mononitrate (B_1)	15 mg.	6.9 lbs. of fried bacon
Riboflavin (B_2)	10 mg.	31½ ozs. of liverwurst
Pyridoxine HCl (B_6)	5 mg.	2 lbs. of yellow corn
Nicotinamide	50 mg.	11 ozs. of roasted peanuts
Calcium pantothenate	10 mg.	¼ lb. of fried beef liver
Ascorbic acid (Vitamin C)	250 mg.	¾ lb. of cooked broccoli

*These common foods are among the richest sources of B vitamins and ascorbic acid. H. A. Wooster, Jr., Nutritional Data, 2nd Ed., Pittsburgh, 1954.

Allbee® with C

Robins

A. H. ROBINS COMPANY, INC.
RICHMOND 20, VIRGINIA

NEW *A.C.M.I.* STERILE PACKAGED

INFLATABLE CATHETERS

- Really dependable sterility
- Always ready—no delay
- For office or bedside

Double protection

...double safety...

ready for instant use

The new A.C.M.I. Sterile Packaged Premium Catheter is double-protected by double packaging, for assured sterility. Even should the durable outer non-peelable package be torn or cut by unduly rough handling, the resilient inner peelable package still protects the sterile catheter from contamination.

Sterilization is achieved under rigidly controlled conditions; and is checked by thorough bacteriological testing before each catheter is released. These catheters more than meet all U.S.P. standards.

FREDERICK J. WALLACE, *President*

American Cystoscope Makers, Inc.

PELHAM MANOR, NEW YORK

for optimal pressor response in

SHOCK

—whatever the clinical situation

INJECTION

ARAMINE®

METARAMINOL

offers a choice of routes...

IN GRAVE EMERGENCIES

- ready as quickly as a syringe can be filled—no need to take the time required to start an infusion
- pressor effect in 1 or 2 minutes after direct intravenous injection

IN LESS GRAVE EMERGENCIES

- therapy can be initiated subcutaneously, intramuscularly, or by intravenous infusion

No sloughing or tissue necrosis reported when injected into preferred veins of arm

Easier maintenance of blood pressure at a constant level—fewer abrupt and excessive responses

Balanced vasopressor, myocardium-stimulating effect

Supplied: in 1-cc. ampuls and 10-cc. vials (10 mg. per cc. present as the bitartrate).

J.A.M.A. **170**:1647 (Aug. 1) 1959 J.A.M.A. **172**:154 (Jan. 9) 1960
J.A.M.A. **171**:1868 (Nov. 28) 1959 Lancet **2**:365-368 (Sept. 19) 1959

Additional information on ARAMINE is available to the physician on request.

ARAMINE is a trademark of Merck & Co., INC.

MSD MERCK SHARP & DOHME • Division of Merck & Co., INC., West Point, Pa.

Index to Advertisers

American Cyanamid Company, Lederle Laboratories Division....23–26, 49, 74, 79, 84, 98, 104, Insert pages 109–110, 118

American Cyanamid Company, Surgical Products Division.....Insert pages 17–20

American Cystoscope Makers, Inc.....123

American Hospital Supply Corporation... 6

American Sterilizer Corporation..... 43

Armour Pharmaceutical Products, Inc.... 53

Astra Pharmaceutical Products, Inc..... 97

Ayerst Laboratories, Inc.....13, 65

C. R. Bard, Inc..... 78

Baxter-Travenol Laboratories, Inc..... 6

Julius Berbecker & Sons, Inc.....104

The Berivon Company..... 84

Bristol Laboratories, Inc. 35, Insert pages 69–72, 111

S. H. Camp & Company..... 66

Castle Company..... 96

Ciba Pharmaceutical Products, Inc..... 68

Clay-Adams, Inc.....105

Codman & Shurtleff, Inc.....118

Cutter Laboratories.....2nd Cover

Davol Rubber Company..... 62

J. A. Deknatel and Sons, Inc..... 99

Desitin Chemical Corp..... 39

Doho Chemical Corp..... 12

Dome Chemical Corp..... 75

Duke Laboratories, Inc..... 84

Eaton Laboratories.....28–29, 33, 45

Eastman Kodak Company....Insert pages 91–92

Electrodyne Co., Inc.....119

Endo Laboratories..... 21

Ethicon, Inc.....4, Insert pages 41–42

Holland-Rantos Company, Inc..... 54

Hyland Laboratories.....113

Identical Form, Inc.....102

Jobst Institute, Inc.....118

Kansas City Assemblage Co..... 98

Knoll Pharmaceutical Company..... 34

Lea & Febiger..... 27

Eli Lilly and Company..... 90

The Mark Company..... 50

The S. E. Massengill Company Insert pages 81–82

Mead Johnson & Company.....86–87

Merck Sharp & Dohme 1, 11, 63, 76–77, 101, 114, 120–121,124–125

Micro X-Ray Recorder, Inc.....104

V. Mueller & Company..... 64

Ohio Chemical & Surgical Equipment Co.. 80

Parke, Davis & Company.46, 55, 67, 94, 106–107

Pfizer Laboratories Insert pages 37–38, 102–103

Poultry and Egg National Board..... 47

A. H. Robins & Company, Inc. 44, 56–59, 100, 122

Roche Laboratories, Division of Hoffmann-La Roche, Inc..... 8

J. B. Roerig and Company.....31, 85

Sanborn Company..... 40

Sandoz Pharmaceuticals..... 16

W. B. Saunders Company.....115

G. D. Searle & Company.....2, 60

J. Sklar Manufacturing Company..... 73

Smith-Dorsey.....108

Smith, Kline & French Laboratories 4th Cover

E. R. Squibb & Sons..... 48

The University of Texas.....114

The Upjohn Company.....10, 32

Wallace Laboratories.....14–15, 22, 83, 89

The Warren-Teed Products Company..... 88

The Waters Corporation..... 98

Wilson Rubber Company..... 36

Winthrop Laboratories, Inc. 61, 93, 112, 3rd Cover

Woodward Medical Personnel Bureau....114

New Alvodine ethanesulfonate

trademark
Brand of piminodine ethanesulfonate

Analgesic potency as great as morphine without drowsiness or hypnosis*

Alvodine, a new and powerful narcotic analgesic, relieves pain as effectively as morphine, yet is much safer because it is free from the high incidence and severity of morphine's side effects. Alvodine is effective *orally* as well as parenterally. Alvodine causes almost no sedation, drowsiness or euphoria. Respiratory and circulatory depression are rare with customary doses; nausea and vomiting are uncommon. Constipation has not been reported.

Preferred agent for specific situations

Alvodine is especially well suited for *postoperative analgesia* because it permits most patients to remain alert and at the same time free from pain. The risk of postoperative pulmonary hypostasis and venous stagnation is decreased because the use of Alvodine allows patients to be mobilized sooner.

Alvodine is ideal for *ambulatory* and *semiambulatory patients* who are in need of strong analgesia. Patients with cancer remain alert and can often carry on their normal daily activities when freed of pain by *oral* doses of Alvodine.

Dosage: Orally, from 25 to 50 mg. every four to six hours as required. By subcutaneous or intramuscular injection, from 10 to 20 mg. every four hours as required.

How Supplied: Alvodine tablets, 50 mg., scored. Alvodine ampuls, 1 cc., containing 20 mg. per cc. *Narcotic Blank Required.*

Winthrop LABORATORIES
New York 18, N. Y.

Write for Alvodine brochure containing detailed information on clinical experience, addiction liability, side effects and precautions.

*In more than 90% of patients.

When your hospitalized patient is tense and nervous

Stelazine® offers these advantages:

brand of trifluoperazine

- low daily doses (2-4 mg.) bring prompt relief—often within 24 to 48 hours
- side effects slight and transitory—rarely interfere with therapy
- often effective where other tranquilizers, muscle relaxants, or sedatives fail

Because 'Stelazine' relieves anxiety with little or no soporific effect, it is particularly useful for your ambulatory patients: presurgical patients, convalescents, patients undergoing diagnostic tests. On 'Stelazine', they usually become calm, relaxed and cooperative—not drowsy and sluggish.

Optimal dosage: 2-4 mg. daily. Available as 1 mg. and 2 mg. tablets, in bottles of 50 and 500.

N.B.: For further information on dosage, side effects, cautions and contraindications, see available comprehensive literature, *Physicians' Desk Reference*, or your S.K.F. representative. Full information is also on file with your pharmacist.

SMITH KLINE & FRENCH

9674